PATENT
Docket No. 030557

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner:	K. J. Puttlitz	
Art Unit:	1621	
In re application of:	Gladysz, et al.	RECOVERY METHOD FOR CATALYSTS, REAGENTS AND CO-PRODUCTS
Serial No.:	10/664,105	
Filed:	September 17, 2003	

DECLARATION OF DENNIS P. CURRAN
UNDER 37 CFR § 1.132

Mail Stop: AF
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Dennis P. Curran, hereby declare and state as follows:

1. I earned a B.S. (Chemistry) from Boston College in 1975 and a Ph.D. (Organic Chemistry) from the University of Rochester in 1979. I am presently a Distinguished Service Professor and the Bayer Professor of Organic Chemistry at the University of Pittsburgh. During my 25 year career at the University of Pittsburgh, I have developed a research program in organic chemistry, including the use of fluorous chemistry (i.e., the chemistry of organic compounds where a high percent of the hydrogens are replaced by fluorines) in organic reactions and separations.

2. I am the author or co-author of approximately 90 peer-reviewed scientific papers on fluorous chemistry and reaction techniques, 11 review articles on fluorous chemistry, and 6 book chapters on fluorous chemistry. I am a co-editor of The Handbook of Fluorous Chemistry (published by Wiley VCH, Weinheim, 2004). I am a listed inventor of 11 United States patents and 10 United States patent applications involving fluorous chemistry or reaction techniques. I am the Founder and Chief Scientific Advisor for Fluorous Technologies, Inc., a company that provides fluorous reagents and products for academic, chemical, and pharmaceutical research.

3. I am one of the listed inventors of the patent application referenced above ("subject application") and of the subject matter described and claimed therein, which claims priority to United States Provisional Application No. 60/411,439 filed September 17, 2002.

4. The subject application discloses and claims methods for conducting a chemical reaction using a fluorous compound in a non-fluorous medium, in the presence of a solid adsorbant containing a fluorous domain and at least one chemical reactant.

5. The Examiner has rejected claims 1-70 under 35 U.S.C § 112, first paragraph, for assertedly failing to reasonably provide enablement for all reactions between a fluorous compound and a chemical reactant. According to the Office Action of December 20, 2005, the Examiner states that the claims broadly recite: all reactions between a fluorous compound and a chemical reactant. The Examiner then states that while the specification and the examples are enabling for hydroalkoxylation and hydrosilation reactions, they do not provide sufficient disclosure that would provide any person skilled in the art guidance to practice the invention, given the infinite amount of possible permutations of the claimed elements.

6. It is my opinion, as one skilled in the art, that the specification discloses and enables the method for conducting a chemical reaction using fluorous chemistry in a non-fluorous medium. In the past, fluorous reactions were limited to mediums or solvent systems that comprised at least one fluorous solvent. This limitation necessitated either disposal or recycling of the fluorous solvent. In contrast, the methods of the subject application describe conducting a chemical reaction using a fluorous compound in a non-fluorous medium, in the presence of a solid adsorbant containing a fluorous domain. The claims of the present invention are not directed to a method of reacting all fluorous reactants, as asserted by the Examiner. Instead, the claims set forth a method of conducting a chemical reaction using a fluorous reactant/catalyst without a fluorous reaction medium, i.e., chemical reactions involving fluorous reactants or catalysts that would normally require a fluorous reaction medium may now be conducted in a non-fluorous medium in the presence of a solid adsorbant containing a fluorous domain using the methods disclosed and claimed in the subject application.

7. It is my view as a person skilled in the art that the specification is enabling for the claimed subject matter and that any person skilled in the art would be able to practice the invention based upon the disclosure in the specification and claims. One skilled in the art could apply the methods claimed in the subject application to known or new fluorous reagents/catalysts for reactions in a non-fluorous medium without undue experimentation.

8. To establish that persons having skill in the art could apply the claimed methods to other systems and fluorous reactions without undue experimentation, based upon the disclosure of the subject application, I submit the following evidence. The initial results on the methods claimed in the subject application were reported by my co-inventors Wende and Gladysz in the *Journal of the American Chemical Society,* **2001**, *123*, 11490-11491

(the "*JACS* Article"), attached hereto as Appendix A. The disclosure in the *JACS* Article along with subsequent discussions led to the provisional application bearing Serial No. 60/411,439 (filed September 17, 2002, less than 1 year after publication of the *JACS* Article) from which the subject application claims priority. The *JACS* Article describes the method for conducting chemical reactions using fluorous catalysis without fluorous solvents based upon thermomorphic properties and liquid/solid phase separation. The *JACS* Article shows the method for conducting the reactions in the presence of a solid adsorbant (i.e., Teflon beads or shavings) (*see*, page 11491, first column, first full paragraph). The *JACS* Article has been cited in numerous papers from research groups studying fluorous reaction systems. Based at least in part on the disclosure of the *JACS* Article, which forms the basis of the present specification and claims, other persons skilled in the art of fluorous reaction systems have successfully applied the methods disclosed therein to other fluorous reagent/catalyst systems without undue experimentation. For example, Bannwarth and co-workers have applied the methods to fluorous palladium catalysts and palladium catalyzed reactions such as the Suzuki coupling and the Sonagashira coupling in a non-fluorous medium, in the presence of a solid adsorbant containing a fluorous domain (*see*, Garcia-Bernabe, A.; Tzschucke, C. C.; Bannwarth, W.; Haag, R., "Supramolecular immobilization of a perfluoro-tagged Pd-catalyst with dendritic architectures and application in Suzuki reactions," *Advanced Synthesis & Catalysis*, **2005**, *347*, 1389-1394 (Appendix B, attached hereto); Tzschucke, C. C.; Bannwarth, W., "Fluorous-silica-supported perfluoro-tagged palladium complexes catalyze Suzuki couplings in water," *Helvetica Chimica Acta* **2004**, *87*, 2882-2889 (Appendix C, attached hereto); and Tzschucke, C. C.; Markert, C.; Glatz, H.; Bannwarth, W., "Fluorous biphasic catalysis without perfluorinated solvents: Application to Pd-mediated Suzuki and

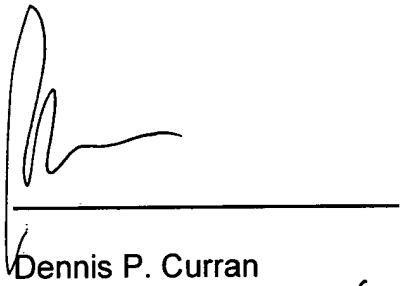
Sonogashira couplings," *Angewandte Chemie, International Edition* **2002**, *41*, 4500-4503 (Appendix D, attached hereto)). In addition, Tsang and co-workers have applied the methods to fluorous tin catalysts and tin catalyzed cyclizations (*see*, Jenkins, P. M.; Steele, A. M.; Tsang, S. C., "Thermoselective phase property of silica tethered with fluorinated chains for controlled 'release' and 'capture' of catalytic fluorous tin species," *Catalysis Communications* **2003**, *4*, 45-50 (Appendix E, attached hereto)). Further, the methods have been discussed in two review articles since its disclosure in the *JACS* Article (*see*, Tzschucke, C. C.; Markert, C.; Bannwarth, W.; Roller, S.; Hebel, A.; Haag, R., "Modern separation techniques for efficient workup in organic synthesis," *Angewandte Chemie, International Edition* **2002**, 41, 3964-4000 (Appendix F, attached hereto) and Horn, J.; Michalek, F.; Tzschucke, C. C.; Bannwarth, W., "Non-covalently solid-phase bound catalysts for organic synthesis," *Topics in Current Chemistry* **2004**, 242, 43-75 (Appendix G, attached hereto)).

9. In my research group, we have successfully applied the methods of conducting a chemical reaction using fluorous chemistry in a non-fluorous medium to fluorous ruthenium catalyzed alkene metathesis reactions (*see*, Matsugi, M.; Curran, D. P., "Synthesis, reaction, and recycle of light fluorous Grubbs-Hoveyda catalysts for alkene metathesis," *Journal of Organic Chemistry* **2005**, *70*, 1636-1642 (Appendix H, attached hereto)). Using the methods claimed in the subject application we have performed alkene metathesis reactions using a fluorous ruthenium catalyst in a non-fluorous medium. The application of the methods to ruthenium catalyzed alkene metathesis did not require undue experimentation.

10. It is my belief that the disclosure in the *JACS* Article, while being significantly less detailed than the disclosure in the subject application, was sufficiently detailed and

enabling to direct the above cited research groups to successfully apply the methods of conducting a fluorous reaction in a non-fluorous medium in the presence of a solid adsorbant containing fluorous domains to other fluorous reagents/catalyst systems, as claimed in the subject application, without undue experimentation. Thus, it is my opinion that the more detailed disclosure of the specification and the examples in the subject application provide sufficient disclosure that enable any person skilled in the art to practice the invention without undue experimentation.

11. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issued thereon.



Dennis P. Curran

March 15, 2006

Date

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Group Art Unit: 1621

Examiner: Karl J. Puttlitz

In re application of
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RECOVERY METHOD FOR CATALYSTS, REAGENTS AND CO-PRODUCTS

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APPENDIX A

Fluorous Catalysis without Fluorous Solvents: A Friendlier Catalyst Recovery/Recycling Protocol Based upon Thermomorphic Properties and Liquid/Solid Phase Separation

Marc Wende, Ralf Meier, and J. A. Gladysz*

Institut für Organische Chemie
Friedrich-Alexander Universität
Erlangen-Nürnberg, Henkestrasse 42
91054 Erlangen, Germany

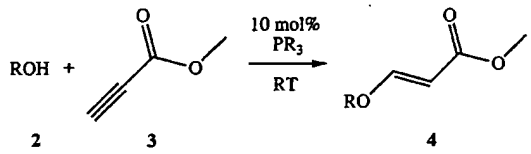
Received June 12, 2001

Over the last 6 years, many new catalysts with high affinities for fluorocarbon (fluorous) solvents have been synthesized.[1,2] This has been prompted by the development of "fluorous biphase catalysis",[1a] which as most often practiced exploits the markedly temperature-dependent miscibilities of organic and fluorous solvents. At room temperature, most combinations give two phases.[3] However, with moderate heating, one phase is obtained. Reactions can be catalyzed under monophasic conditions at the high-temperature limit and the products and catalyst separated under biphasic conditions at the low-temperature limit.

No catalyst recovery method is without potential drawbacks.[4] Accordingly, the fluorous solvent requirement in this protocol has mobilized a vocal contingent of nay-sayers, the major objections from which involve cost and environmental persistence.[3] However, a way to eliminate any such problems has been overlooked. High fluorous-phase affinities are achieved by appending a number of "pony tails" $(CH_2)_m(CF_2)_{n-1}CF_3$ (typically $m = 0-3$, $n = 6-10$) to the catalyst, often giving a low-melting solid. What has not been appreciated is that the same factors that give highly temperature-dependent organic/fluorous *liquid/liquid* phase miscibilities can also give highly temperature-dependent organic/fluorous *liquid/solid* phase miscibilities (e.g., solubilities). In less conceptual terms, as we gained more and more experience with pony-tail-containing fluorous compounds in our laboratory, we began to notice marked increases in solubilities with temperature, particularly near melting points.

A case in point is the easily prepared fluorous phosphine $P((CH_2)_2(CF_2)_7CF_3)_3$ (**1**), which melts at 47 °C.[5] As part of a study involving many related phosphines,[5,6] we began to probe various types of phosphine-catalyzed organic reactions already in the literature.[7,8] The addition of alcohols **2** to methyl propiolate (**3**) shown in Chart 1 was selected for emphasis.[8] Good yields of addition products **4** were obtained at room temperature with both

Chart 1. Phosphine-Catalyzed Addition Reaction



1 = $P((CH_2)_2(CF_2)_7CF_3)_3$

	ROH (0.9 equiv)	Catalyst	Solvent	Yield (%)	Time (h)
2a	$PhCH_2OH$	**1**	$CF_3C_6H_5$	90 [a]	24
				95 [a]	96
		$P(n\text{-}Bu)_3$	CH_2Cl_2	72 [b]	0.5
2b	Ph_2CHOH	**1**	$CF_3C_6H_5$	78 [a]	48
		$P(n\text{-}Bu)_3$	CH_2Cl_2	85 [b]	0.5
2c	$PhCH(CH_3)OH$	**1**	$CF_3C_6H_5$	81 [a]	24
		$P(n\text{-}Bu)_3$	CH_2Cl_2	89 [b]	0.5
2d	$CH_3(CH_2)_7OH$	**1**	$CF_3C_6H_5$	86 [a]	48
		$P(n\text{-}Bu)_3$	CH_2Cl_2	77 [b]	0.5

[a] GC yield (vs internal standard); starting concentrations: 0.3 M (**2b**) or 0.5 M (**2a, c, d**). [b] Isolated yield after Kugelrohr distillation (≥98% purity); starting concentrations: 1.5 M (**2b**) or 1.0 M (**2a, c, d**).

a previously reported catalyst system, $P(n\text{-}Bu)_3$ in CH_2Cl_2, and **1** in $CF_3C_6H_5$. The latter solvent was selected for its ability to dissolve both fluorous and nonfluorous compounds.[9] The mechanism is believed to involve initial 1,4-addition of the phosphine to give a zwitterionic allenolate, which then deprotonates the alcohol.[8a] An alkoxide addition/phosphine elimination sequence gives the product and regenerates the catalyst. Reactions should be slower in less polar solvents, consistent with the data in Chart 1. $P(n\text{-}Bu)_3$ was also an effective catalyst in $CF_3C_6H_5$ and gave faster rates than **1**, consistent with its greater basicity and nucleophilicity.[6d]

We were able to recycle catalyst **1** using standard liquid biphase (e.g., $CF_3C_6F_{11}$/octane) and monophase ($CF_3C_6H_5$) conditions, as will be detailed in a full paper. Of particular novelty and the emphasis of this communication is the thermomorphic[10] behavior shown in Figure 1. Between 20−80 and 20−100 °C, **1** exhibits ca. 60- and 150-fold increases of solubility in octane. Although octane is one of the best organic solvents for dissolving nonpolar fluorous compounds, little **1** could be detected at 0 °C by GC (0.31 mM) or ^{31}P NMR. At 20 °C, millimolar concentration levels were present (1.13 mM, GC; 0.97 mM, NMR). A distinct jump in solubility was observed near the melting point (19.6 mM, 50 °C), followed by continued increases (63.4 mM, 80 °C; 157 mM, 100 °C).

Such a dramatic solubility/temperature dependence suggests an obvious catalyst recycling method. As shown in Chart 2, **1** (0.1 equiv), **2a** (2.0 equiv), and **3** were combined in octane (65.0 mM in **3**). The sample was kept at 65 °C (8 h) and cooled to −30 °C (arbitrary temperature of a convenient freezer). The precipitated catalyst (in some cases orange-colored) was isolated by decantation. GC analysis of the supernatant indicated a 82%

(1) (a) Horváth, I. T. *Acc. Chem. Res.* **1998,** *31,* 641. (b) Cavazzini, M.; Montanari, F.; Pozzi, G.; Quici, S. *J. Fluorine Chem.* **1999,** *94,* 183. (c) Bhattacharyya, P.; Croxtall, B.; Fawcett, J.; Fawcett, J.; Gudmunsen, D.; Hope, E. G.; Kemmitt, R. D. W.; Paige, D. R.; Russell, D. R.; Stuart, A. M.; Wood, D. R. W. *J. Fluorine Chem.* **2000,** *101,* 247.

(2) Full papers with extensive literature background: (a) Horváth, I. T.; Kiss, G.; Cook, R. A.; Bond, J. E.; Stevens, P. A.; Rábai, J.; Mozeleski, E. J. *J. Am. Chem. Soc.* **1998,** *120,* 3133. (b) Juliette, J. J. J.; Rutherford, D.; Horváth, I. T.; Gladysz, J. A. *J. Am. Chem. Soc.* **1999,** *121,* 2696. (c) Richter, B.; Spek, A. L.; van Koten, G.; Deelman, B.-J. *J. Am. Chem. Soc.* **2000,** *122,* 3945. (d) Zhang, Q.; Luo, Z.; Curran, D. P. *J. Org. Chem.* **2000,** *65,* 8866.

(3) Survey of practical considerations and underlying physical principles: Barthel-Rosa, L. P.; Gladysz, J. A. *Coord. Chem. Rev.* **1999,** *190−192,* 587.

(4) For an essay on the "ideal recoverable catalyst", see: Gladysz, J. A. *Pure Appl. Chem.* **2001,** *73,* 1319.

(5) Alvey, L. J.; Rutherford, D.; Juliette, J. J. J.; Gladysz, J. A. *J. Org. Chem.* **1998,** *63,* 6302.

(6) (a) Alvey, L. J.; Meier, R.; Soós, T.; Bernatis, P.; Gladysz, J. A. *Eur. J. Inorg. Chem.* **2000,** 1975. (b) Klose, A.; Gladysz, J. A. *Tetrahedron Asymmetry* **1999,** *10,* 2665. (c) Soós, T.; Bennett, B. L.; Rutherford, D.; Barthel-Rosa, L. P.; Gladysz, J. A. *Organometallics* **2001,** 20, 3079. (d) Jiao, H.; Soós, T.; Meier, R.; Le Stang, S.; Rademacher, P.; Kowski, K.; Jafarpour, L.; Hamard, J.-B.; Nolan, S. P.; Gladysz, J. A. submitted to *J. Am. Chem. Soc.*

(7) The Bayliss−Hillman reaction is one extensively studied example. See: (a) Buono, G.; Chiodi, O.; Wills, M. *Synlett* **1999,** 377. (b) Lu, X.; Zhang, C.; Zu, Z. *Acc. Chem. Res.* **2001,** *34,* 535. (c) Vedejs, E.; Daugulis, O.; Mackay, J. A.; Rozners, E. *Synlett* **2001,** 1499.

(8) (a) Inanaga, J.; Baba, Y.; Hanamoto, T. *Chem. Lett.* **1993,** 241. (b) R. Meier, Ph.D. Thesis, Universität Dortmund, 1998.

(9) Maul, J. J.; Ostrowski, P. J.; Ublacker, G. A.; Curran, D. P. *Top. Curr. Chem.* **1999,** *206,* 79.

(10) Bergbreiter, D. E.; Osburn, P. L.; Wilson, A.; Sink, E. M. *J. Am. Chem. Soc.* **2000,** *122,* 9058 and references therein.

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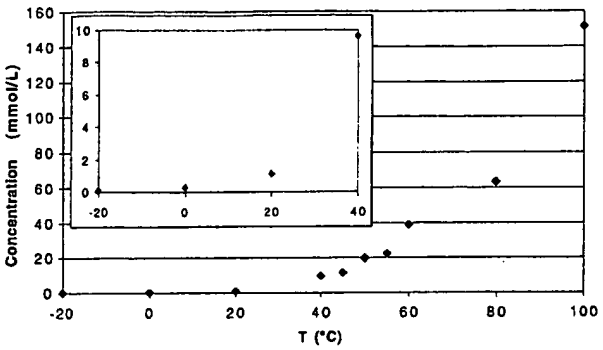


Figure 1. Temperature-dependent solubility of $P((CH_2)_2(CF_2)_7CF_3)_3$ (**1**) in octane (GC vs internal standard; ≥15 min stirring at each temperature and ≥5 min settling period with no stirring).

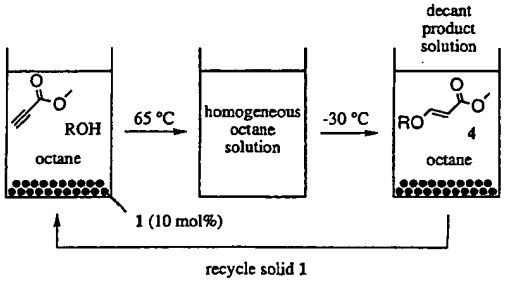
yield of **4a**. The recovered catalyst was used for four further cycles without deterioration in yield, as summarized in Chart 2. Similar results were obtained with alcohols **2b-d**. No background reactions were detected at 65 °C in the absence of **1**, and rates were much slower at lower temperatures.

In a procedural variation, identical reactions were conducted in the presence of Teflon beads or shavings. This provided an adsorbant for the precipitated catalyst, and physically facilitated recycling. The Teflon/catalyst residue from such an experiment (synthesis of **4a**) was extracted with $CF_3C_6H_5$, and a known amount of PPh_3 was added. A ^{31}P NMR spectrum indicated a 89.5% recovery of **1** and 7.8% of two new phosphorus-containing species (possibly educt-derived alternative rest states). The octane solution of the product showed a barely integratable signal for the oxide of **1** (0.4% leaching).[5]

In a further refinement, **2a** and **3** were reacted as in Chart 2, but in the absence of solvent. Toluene was added to efficiently separate **4a** from solid **1**, which was then reused. Yields for a four-cycle sequence were 99, >99, 97, and 95%. The temperature dependence of the solubility of **1** in toluene was also probed. At 0 and 20 °C, concentrations were similar to those in octane. However, solubilities were reduced by half at 40 and 45 °C (4.00 and 5.56 mM), and rose to only 14.4 M at 80 °C. We view this as a logical consequence of the higher solvent polarity and speculate that more dramatic gradients can be achieved with shorter pony tails.

We believe that one-solvent protocols of the type described above will be applicable to a wide variety of fluorous catalysts. It is probably not always necessary to traverse a melting point to achieve a sufficient solubility gradient. Nonetheless, one would expect that the melting points of fluorous compounds can be engineered by shortening, lengthening, or branching the pony tails and by increasing/decreasing their numbers. The phase properties

Chart 2. Fluorous Catalyst Recycling Based upon Liquid/Solid Phase Separation



ROH (2.0 equiv)[a]	Cycle	Yield (%)
2a	1	82
	2	82
	3	80
	4	81
	5	75
2b	1	77
	2	84
	3	71
2c	1	90
	2	86
	3	75
2d	1	79
	2	84
	3	66

[a] Starting concentration of **2**: 1.25 M; reaction time: 8 h; reaction temperature: 65 °C.

of a catalyst family could be optimized and tailored to a broad portfolio of solvents. However, it must be emphasized that the solubility characteristics of the *catalyst rest state*—not the catalyst precursor—are critical for recycling. In Charts 1 and 2, phosphine **1** represents the dominant rest state, but transition-metal catalyst precursors often exhibit induction periods or are otherwise transformed under reaction conditions. In any event, we have unequivocally shown that fluorous catalysts can be utilized under one-phase conditions in ordinary organic solvents and recovered by low-temperature liquid/solid-phase separation[11] and without recourse to fluorous solvents. There are obvious further refinements of our methodology, and these will be reported in due course.

Acknowledgment. We thank the Deutsche Forschungsgemeinschaft (DFG; GL 300-3/1) for support (liquid/liquid biphase experiments).

JA011444D

(11) For a complementary approach to designing liquid/solid-phase separations, see: Bosanac, T.; Yang, J.; Wilcox, C. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 1875; *Angew. Chem.* **2001**, *113*, 1927.

APPENDIX B

Supramolecular Immobilization of a Perfluoro-Tagged Pd-Catalyst with Dendritic Architectures and Application in Suzuki Reactions

Abel Garcia-Bernabé,[a] Carl Christoph Tzschucke,[b] Willi Bannwarth,[b,*] Rainer Haag[c,*]

[a] Departamento de Termodinámica Aplicada, Universidad Politécnica de Valencia, camino de Vera s/n,46022 Valencia, Spain
[b] Institut für Organische Chemie und Biochemie, Albert-Ludwigs-Universität Freiburg, Albertstrasse 21, 79104 Freiburg, Germany
E-mail: willi.bannwarth@organik.chemie.uni-freiburg.de
[c] Institut für Chemie, Freie Universität Berlin, Takustrasse 3, 14195 Berlin, Germany
Fax: (+49)-30-838-53357; e-mail: haag@chemie.fu-berlin.de

Received: February 7, 2005; Accepted: May 13, 2005

Abstract: A new supramolecular complex of a perfluoro-tagged palladium phosphine catalyst to a dendritic core-shell architecture with a perfluoroalkyl shell was used as recoverable catalyst for Suzuki couplings. This homogeneous complex can also serve as a model for related catalysts adsorbed on fluorous silica gel.

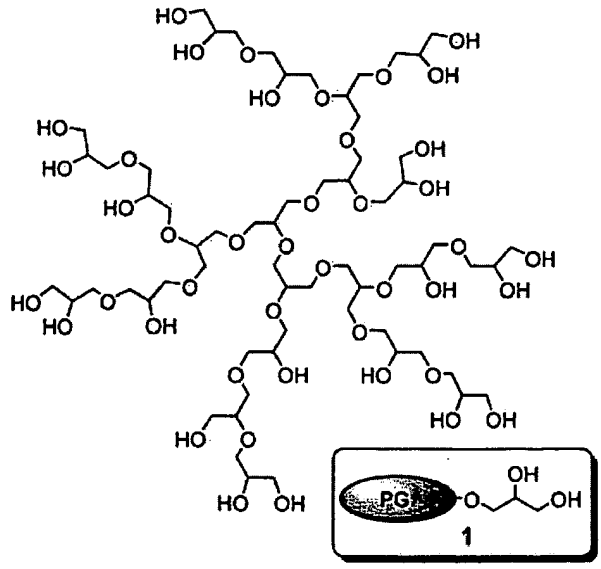
Keywords: dendrimers; fluorinated ligands; ligand recycling; palladium catalysis; supramolecular complex; Suzuki coupling

Introduction

Dendritic core-shell architectures have attracted increasing interest for their ability to act as unimolecular nanocarriers for catalysts, pharmaceuticals and other guest molecules.[1] More recently, such nanostructures have also been prepared with perfluorinated shells[2,3] allowing easy recovery of products and recycling of catalytic nanoparticles in alternative reaction media, such as $scCO_2$ and perfluorinated solvents.[4]

For many applications the difficult accessibility of dendrimers *via* costly multistep syntheses represents a major problem.[5] Hyperbranched polymers that can be obtained in one reaction step from the polymerization of AB_m monomers are currently being discussed as possible alternatives.[6] In contrast to the perfectly branched glycerol dendrimers (DB = 100%),[3,7] hyperbranched polyglycerols (PG) **1** are randomly branched, but well-defined dendritic structures with a degree of branching of approx. 60%. They are prepared in a one-step process and are readily available on a kilogram scale with relatively low molecular weight distributions (typically < 2).[8]

For the covalent immobilization and the recycling of homogeneous catalysts dendritic polymers have been used by many groups.[9] However, only a few examples have been reported for the non-covalent anchoring of catalysts in dendritic architectures by supramolecular interactions.[10] In these cases, the linkage between the transition metal complexes and the dendritic support is based on, e.g., ionic interactions in combination with multiple hydrogen bonds and allows a high degree of flexibility.



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Yet another approach for the non-covalent immobilization of catalysts has been presented by one of our groups who used interactions between fluorous phase silica (FPS) and perfluoro-tagged palladium complexes for the immobilization and recycling of catalysts in organic solvents.[11] In this heterogeneous system the efficient catalysis, the catalytic properties and the quantitative catalyst recovery by simple filtration were demonstrated for various C–C coupling reactions. Due to the heterogenic nature of this system it is quite difficult to analyze the catalytic process in detail. Therefore, a homogeneous analogue of this catalytic system should allow us to get more insight into the active catalytic species and the supramolecular interactions by NMR techniques.

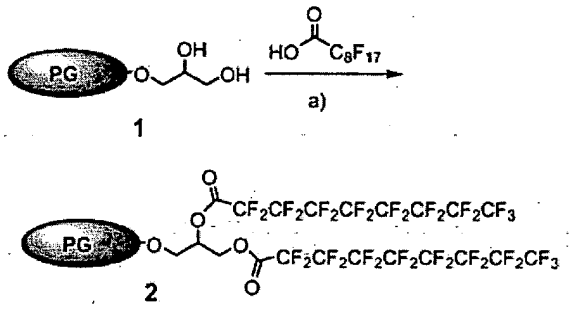
Recently, we have reported on the syntheses of novel dendritic architectures with perfluorinated shells derived from the covalent modification of perfect glycerol dendrimers, hyperbranched polyglycerols and hyperbranched polyethyleneimines.[3] These polymers are soluble in several perfluorinated solvents and can encapsulate ions, polar dyes and metal nanoparticles. However, we were not able to perform catalytic reactions in the presence of these systems. This is probably due to complexation and inactivation of Pd by the presence of chelating S- or N-ligands in these dendritic polymers. Thus, we herein present a nitrogen- and sulfur-free dendritic structure based on a dendritic architecture built from polyglycerol core and a perfluoroalkyl shell. This system was used as supramolecular support to immobilize a perfluoro-tagged catalyst and study its catalytic activity in Suzuki coupling reactions as well as the complex stability.

Results and Discussion

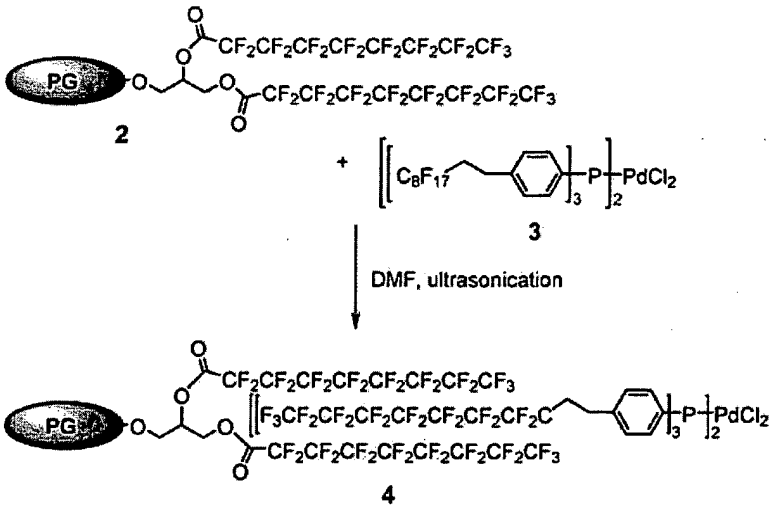
For the preparation of the dendritic core-shell-type architecture, we esterified hyperbranched polyglycerol **1** ($M_n = 5000$ g mol^{-1})[8] with a perfluorinated carboxylic acid by azeotropic distillation (Scheme 1). This fluorophilic nanocarrier was prepared on a multigram scale and was easily purified with a strongly basic anion exchange resin (4 mmol OH^-/g) to yield 85% of PG-perfluoroester **2**. The degree of functionalization obtained from ^{13}C NMR (inverse gated) was 47%.

Then the perfluoro-tagged palladium phosphine complex **3**,[12] meanwhile commercially available (Fluka), was immobilized in the perfluorinated shell of the dendritic polyglycerol ester to obtain the supramolecular architecture **4** simply by dissolution of both components in DMF with ultrasonication (Scheme 2).

The strong interaction between the perfluorinated chains in the supramolecular complex **4** was observed by ^{19}F NMR spectroscopy (Figure 1). The spectrum



Scheme 1. Synthesis of dendritic polyglycerol perfluoroalkyl ester **2** from hyperbranched polyglycerol **1**; a) pTSA cat., BTF, azeotropic distillation, 3 days.



Scheme 2. Supramolecular interaction between perfluoro-tagged palladium complex **3** and polyglycerol ester **2**.

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shows an isolated CF_3 signal at -83.31 ppm. Upon complex formation a significant amount of the CF_3 signal undergoes a high-field shift of 1.70 ppm to -81.61 ppm. This shift of the CF_3 signal is characteristic for the partial intercalation of perfluoroalkyl chains and has also been observed for other supramolecular aggregates as well as for the self-aggregation of perfluoroalkyl-modified perfect dendrimers.[13] It is noteworthy for the catalytic action of the immobilized catalyst that the fluorous-fluorous interaction is temperature dependent and is reduced significantly at higher temperatures (Figure 2). This will enhance the flexibility of the ligand and hence increase its catalytic activity. This temperature-dependent aggregation might also explain the excellent results of the heterogeneous system consisting of perfluoro-tagged Pd catalysts adsorbed on fluorous silica gel.[11] In this case we now have a strong indication for the formation of a homogeneous catalytic species, which might be due to the temperature-dependent desorption of the catalyst from the solid support at elevated temperature (80 °C), while a strong insoluble complex is present at room temperature.

We also obtained TEM images of the supramolecular aggregate **4** (Figure 3). The image shows spherical particles with a diameter of approx. 3 ± 2 nm. This corresponds to the size expected for single molecules of the dendritic perfluoroalkyl ester **2**, however, a micellar assembly of a few particles cannot be excluded due to the error of the TEM measurement. But the particles are certainly small enough to be homogeneously dissolved in solution.

The catalytic activity of immobilized perfluoro-tagged palladium complex **4** was now studied in homogeneous Suzuki coupling reactions (Scheme 3) and compared

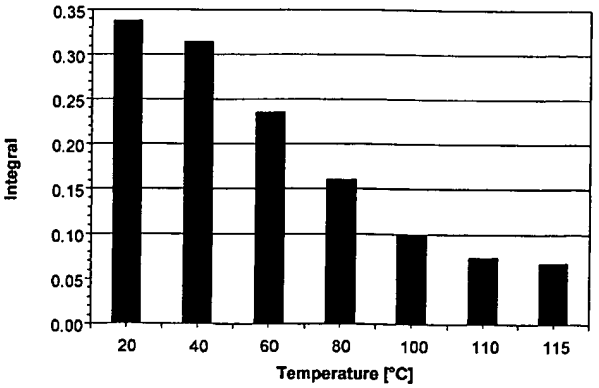

Figure 2. Temperature-dependence of the CF_3-group integral of the complex **4** at -83.31 ppm in DMF.

to the perfluoro-tagged catalyst itself at different catalyst concentrations (Table 1). For these studies a 1:1 molar ratio of polyglycerol ester **2**/perfluoro-tagged Pd catalyst **3** was used.

Initially, we tried to use a mixture of dimethoxyethane (DME) and water as solvent system similar to the heterogeneous FSG-system.[11] However, the supramolecular catalyst **4** was not soluble in this mixture. We only observed homogeneous reaction conditions when using DMF as a solvent. An advantage of this selective solubility is that the supported catalyst **4** can easily be recycled by precipitation in a mixture of DME/water (10% HCl) 2:1, whereas the substrate and product remain soluble in this mixture. The precipitated catalyst complex **4** was filtered and re-used for three consecutive Suzuki coupling reactions. Each reaction series was performed at three different catalyst loadings 0.1, 0.5 and 1 mol %

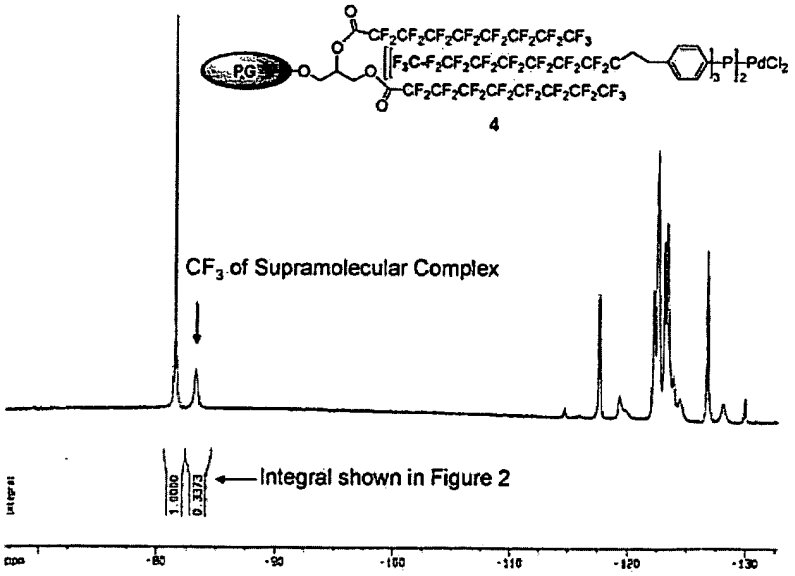

Figure 1. ^{19}F NMR spectra of supramolecular complex **4** in DMF at 20 °C.

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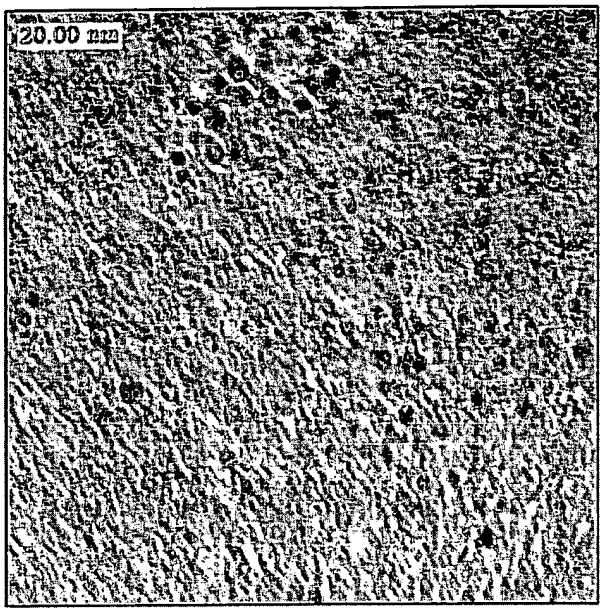
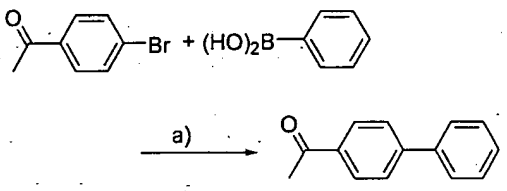


Figure 3. TEM image of the supramolecular complex **4**. The bar in the TEM image is equivalent to 20 nm.



Scheme 3. Suzuki coupling reaction performed with the supramolecular palladium complex **4**. a) 0.1, 0.5 and 1 mol % catalyst (see Table 1), Na_2CO_3, DMF, 80 °C, 20 h.

(Table 1). The pure product can easily be obtained by extraction of the soluble phase with chloroform/water. After concentration of the chloroform layer the conversion yield was determined from the ^1H NMR spectra by integration of the methyl signals.

We have also tested the catalytic activity of the perfluoro-tagged palladium catalyst without the dendritic support **2** under the same conditions (Table 1). While Gladyzs et al. demonstrated that it is possible to use fluorous catalysts in the absence of fluorous solvents provided the perfluoro-tagged catalyst is sufficiently soluble at the reaction temperature,[14] in our case, perfluoro-tagged palladium is also catalytically active in DMF, but the yields without support **2** are significantly lower than the reactions of the supramolecular assembly **4**. This is probably due to the fact that the Pd complex **3** alone is not soluble in DMF, whereas the supramolecular assembly **4** is soluble. It is also noteworthy that a catalyst loading of 0.1 mol % is sufficient for a single run, however, for multiple use higher concentrations of the complex **4** are needed (Table 1). The high catalytic activity of this supramolecular complex **4** can be explained by its relative small particle size (3 ± 2 nm) and the homogeneous reaction conditions. Thus, the dendritic support serves to molecularly disperse the Pd complex in the reaction mixture.

With regard to our earlier experiments with perfluoro-tagged Pd complexes adsorbed on fluorous silica gel, the supramolecular complex **4** can be used as a homogeneous model system to explain the observed reactivity.[11] We assume that the way these two catalytic systems act is similar and in both cases the release of the perfluoro-tagged Pd-catalyst occurs at high temperature, while a strong complex is present at room temperature. Therefore, also the fluorous solid phase acts in the same way as the fluorous dendritic polymer, namely to disperse the perfluoro-tagged catalyst and bring a large portion of it into homogeneous contact with the reaction mixture, in which the heterogeneous FPS remains insoluble.

Conclusion

In summary, we have immobilized a perfluoro-tagged palladium catalyst on a dendritic polyglycerol ester with a perfluorinated shell **2** and investigated its catalytic activity in Suzuki couplings. The supported catalyst **4** can be separated from the product by simple precipitation using a mixture of DME/water. The dendritic support allows for a better solubility of the perfluoro-tagged palladium complex in organic solvents and increases the yield of the reaction significantly. Also, the recycling and multiple use of this supramolecular catalyst **4** is straightforward. This demonstrates a new concept for dissolving perfluoro-tagged catalysts in the usual organic solvents and for allowing their separation and recovery by precipitation. Furthermore, this supramolecular dendritic assembly serves as a valuable soluble model for the interaction of perfluoro-tagged catalysts with insoluble supports such as fluorous silica gel and clearly reveals the ligand diffusion from the complex at elevated tem-

Table 1. Results of consecutive Suzuki couplings.

Catalyst loading [mol%]	Yield [%] (1st run)	Yield [%] (2nd run)	Yield [%] (3rd run)	Yield [%] without support **2**
0.1	>99	29	3	26
0.5	>99	>99	97	29
1	>99	>99	>99	55

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peratures. This behavior can also explain the high catalytic activity of the heterogeneous FPS system.

Experimental Section

Synthesis of Polyglycerol Perfluorononanoic Ester (2)

A suspension of hyperbranched polyglycerol (M_n = 5000 g mol^{-1}) (0.315 g, 4.3 mmol of hydroxy groups),[8] 2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,9-heptadecafluorononanoic acid (2 g, 4.3 mmol) and para-toluenesulfonic acid (pTSA) (0.105 g, 0.7 mmol) in a mixture of toluene (40 mL) and α,α,α-trifluorotoluene (BTF) (20 mL) was heated to reflux for 3 days. The water was removed by azeotropic distillation. After reaction the solvent was removed by evaporation and the residue was redissolved in perfluorobenzene (5 mL). To this solution 1.2 g of basic anion exchange resin, Merck (4 mmol OH^-/g) was added and stirred for 4 hours. The resin was removed by filtration and the solvent was evaporated in vacuum to obtain a brownish viscous polymer **2**, yield: 1.118 g (85%). ^{1}H NMR (400 MHz, C_6F_6/$CDCl_3$): δ = 3.2–5 (m, CH_2O, CHO), 5.5 (m, CH_2O, CHO); ^{13}C NMR (100 MHz, C_6F_6/$CDCl_3$): δ = 65.7 (m, CH_2O), 67.8 (m, CH_2O), 68.7 (m, CH_2O), 69.7 (m, CH_2O), 72.3 (m, CH_2O), 74.3 (m, CH_2O), 79.6 (m, CH_2O), 106.2 (m, CF_2), 108.2 (m, CF_2), 111.6 (m, CF_2), 113.8 (m, CF_2), 116.3 (t, CF_2, $^1J_{F\text{-}C}$ = 30 Hz), 119.2 (t, CF_2, $^1J_{F\text{-}C}$ = 30 Hz), 122.0 (m, CF_2), 128.1 (m, CF_2), 130.4 (m, CF_2), 106.2 (m, CF_2), 108.9 (m, CF_2), 111.6 (m, CF_2), 158.6 (m, OCO).

General Procedure for Suzuki Coupling Reactions

A 0.001 M solution of perfluoro-tagged catalyst **3** (10 mg, 0.003 mmol) and the dendritic perfluoroester **2** (60 mg, 0.003 mmol) in 3 mL of absolute DMF was prepared by ultrasonification for 30 min. Then one equivalent 4-bromoacetophenone, 1.1 equivalent of phenylboronic acid and 2.5 equivalent of sodium carbonate were added under argon. The reaction mixture was heated to 80 °C for 20 hours. The solvent was evaporated and the residue was dissolved again with a mixture of dimethoxyethane (DME) and water (10% HCl) (2:1). The insoluble part was filtered, washed with DME/water (2:1) and recycled for the next run (recovery yield ca. 50%). The combined DME/water layers were concentrated in vacuum and extracted three times with chloroform-water. Evaporation of the combined chloroform layers gave the product. The conversion yield was calculated from the methyl signals in the ^{1}H NMR spectra (product/substrate).

Acknowledgements

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APPENDIX C

Fluorous-Silica-Supported Perfluoro-Tagged Palladium Complexes Catalyze *Suzuki* Couplings in Water

by **Carl Christoph Tzschucke** and **Willi Bannwarth***

Institut für Organische Chemie und Biochemie, Albert-Ludwigs-Universität Freiburg, Albertstrasse 21, D-79104 Freiburg

(phone: +49 761 2036073; fax: +49 761 2038705; e-mail: willi.bannwarth@organik.chemie.uni-freiburg.de)

Different Pd-complexes (see **2a–d** and **3**) with and without perfluoroalkyl tags were deposited on fluorous reversed-phase silica **1** and unmodified silica gel. These supported complexes were successfully used as precatalysts for the *Suzuki* reaction in H_2O. H_2O-Soluble aryl bromides were easily converted to the corresponding biphenyls. Although none of the complexes is H_2O-soluble, the active catalyst is most likely homogeneously dissolved. Nevertheless, the Pd-leaching into the product was low.

Introduction. – In catalytic chemistry, there is an increasing requirement to optimize reactions in terms of environmental and process safety as well as in terms of economic viability. Important aspects are the reduction of waste, straightforward isolation of products, recycling of catalysts, and the use of environmentally benign reaction media [1]. Water is in these regards a suitable solvent, since it is cheap, nonflammable and nontoxic. However, it is important to remove products and catalyst efficiently to allow for easy disposal of H_2O.

Solid-supported catalysts have become valuable tools for simplified product isolation and catalyst recycling. For immobilization, catalysts can be linked covalently to different supports, such as polymer resins or inorganic solids. Polar catalysts can be adsorbed on silica gel [2], or immobilized in a thin layer of H_2O [3], ethylene glycol [4], or ionic liquids [5][6] on a silica support. The reaction is carried out in an apolar organic solvent. These applications usually require suitable derivatization of the catalyst with polar functionalities. The system can be reversed in such a way that a lipophilic catalyst is physisorbed on reversed-phase silica gel [7] or fluorous reversed-phase silica gel (FRPSG) [8][9] and applied to reactions in polar solvents.

In this context, we reported the use of fluorous reversed-phase silica gel (FRPSG) as solid support for the noncovalent immobilization of perfluoro-tagged Pd-catalysts [8]. These supported Pd-complexes were applied to *Suzuki* couplings and to *Sonogashira* reactions. The FRPSG-supported catalyst was removed by simple decantation or filtration, and the catalyst could be reused several times without significant loss of efficiency. The same strategy was used in a solventless approach by *Biffis et al.* for the immobilization of dirhodium(II) perfluorocarboxylates as catalyst for the alcoholysis of silanes [9]. Attempts of *Pozzi et al.* to immobilize perfluoro-tagged [Co^{III}(salen)] complexes on FRPSG did not lead to active catalysts [10]. In a similiar context, *Gladysz et al.* employed the thermomorphic behavior of certain perfluoro-tagged compounds together with *Teflon* shavings as solid-support material

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[11–13]. In combinatorial chemistry, FRPSG has been used as a solid support for multistep organic synthesis [14]. FRPSG has found numerous applications as material for solid-phase extractions and chromatography [15][16].

While, in our previous experiments in 1,2-dimethoxyethane (=glyme), the Pd-leaching was already low [8], we thought that it could be further reduced by the use of H_2O as the reaction solvent, because of the pronounced hydrophobicity of perfluoro-tagged compounds. But this hydrophobicity also presents a challenge, since FRPSG is usually not wetted by H_2O as demonstrated by the high contact angle (*Fig. 1*) [17], and the question was whether the reaction could occur at all. Herein, we report the first application of a precatalyst supported on FRPSG in H_2O as the sole reaction solvent, and data suggesting a homogeneous nature of the actual catalytic species.

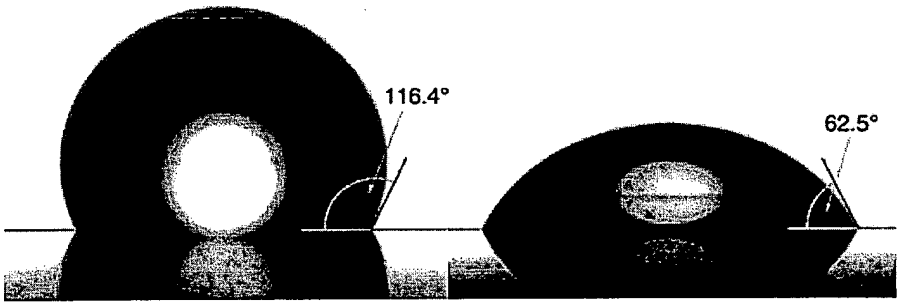
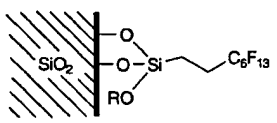
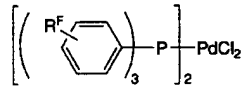


Fig. 1. *Photographs of solvent drops on the perfluorinated silicium dioxide surface of a silicon wafer, demonstrating the large difference in polarity:* left: *water drop with a contact angle of 116.4°, and* right: *1,2-dimethoxyethane drop with a contact angle of 62.5°.* Due to the lower interfacial energy, 1,2-dimethoxyethane can wet FRPSG much better than H_2O [17].

Results and Discussion. – The FRPSG **1** and the perfluoro-tagged Pd-complexes **2a–d** were prepared by our reported procedures [14][18]. For the immobilization of the complexes, FRPSG **1** was shaken with a solution of perfluoro-tagged bis(triarylphosphine)palladium complexes **2a–d** in Et_2O, and the solvent was evaporated. The thus immobilized precatalyst is an air-stable, free-flowing powder. These catalyst-loaded FRPSGs were employed in different *Suzuki* cross-coupling reactions in H_2O.



1



2a $R^F = 4\text{-}C_8F_{17}CH_2CH_2$
2b $R^F = 3\text{-}C_8F_{17}CH_2CH_2$
2c $R^F = 4\text{-}C_8F_{17}$
2d $R^F = 4\text{-}C_7F_{15}CH_2O$
3 $R^F = H$

Initially, between 0.001 mol-% and 1 mol-% of **2a** on FRPSG was tested as precatalyst for the *Suzuki* coupling of phenylboronic acid and *p*-bromomandelic acid (=4-bromo-α-hydroxybenzeneacetic acid) in H_2O (see *Scheme 1* and *Table 1*). The product was separated by filtration, and the supported catalyst was reused up to five times. For the higher catalyst loadings (*Entries 1* and *2*), nearly complete conversion was observed in the first run. Up to the sixth run, the conversion decreased only to 87% and 76%, respectively. With the lower catalyst loadings (*Entries 3* and *4*), the conversion was low in the first run but increased significantly in the second run. It must be noted, however, that the yields deviate more from the average in the first runs than in the following runs. This might be due to insufficient wetting of the support during the first run. The conversions remained on a fairly high level with 0.01 mol-% of catalyst. Only with 0.001 mol-% of catalyst, the conversions decreased from the third to the sixth run, still leading to cumulated turn-over numbers (TON) of more than 200000.

Scheme 1. Suzuki *Reactions Performed with 0.01–1 mol-% of* **2a** *Immobilized on Support* **1**

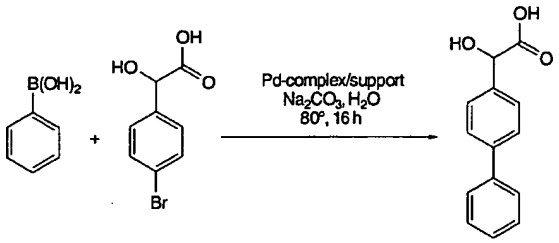


Table 1. Suzuki *Reactions with Complexes* **2a–d** *and* **3**. Yields are determined by HPLC and are the average of at least two independent experiments. TON = turn-over number.

Entry	Catalyst/Support	Catalyst loading [mol-%]	Yield [%]	TON
1	**2a**/FRPSG	1.0	98 (98, 95, 90, 83, 87)	551
2	**2a**/FRPSG	0.1	99 (91, 88, 79, 80, 76)	5130
3	**2a**/FRPSG	0.01	6 (74, 86, 86, 85, 70)	40600
4	**2a**/FRPSG	0.001	27 (71, 54, 37, 22, 7)	217000
5	**2b**/FRPSG	0.1	88 (62, 83, 84, 86, 82)	4850
6	**2c**/FRPSG	0.1	94 (76, 83, 82, 74, 73)	4820
7	**2d**/FRPSG	0.1	85 (90, 89, 88, 85, 75)	5120
8	**3**/silica gel	0.1	52 (95, 95, 91, 85, 77)	4950

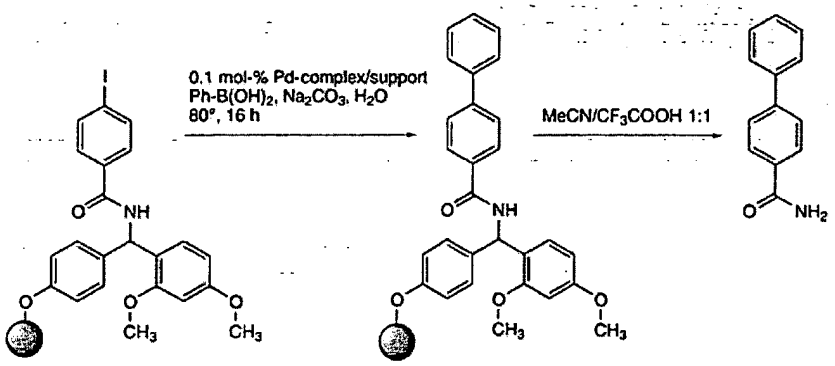
To examine the influence of the perfluoro tags and the support, Pd-complexes **2b–d** and **3** on FRPSG **1** were used as precatalysts. Like in complex **2a**, in **2b** an ethylene spacer isolates the aryl ring from the electron-withdrawing perfluoroalkyl chain. In **2c** the perfluoro tag is directly attached to the phenyl ring, while, in **2d**, an electron-donating CH_2O spacer is employed. In these experiments, the loading of the support was 10 mg of complex per g FRPSG, and the catalyst loading was 0.1 mol-%. In the first run, the yields obtained with **2b–d** were slightly lower than with **2a**, but in recycling experiments, all four complexes behaved similarly, giving cumulated TONs in the range of 5000 (*Table 1*, *Entries 5–7*). Thus, neither the spacer between the perfluoroalkyl chain and the phenyl ring nor the point of attachment of the perfluoro tag exerts a

detectable influence on the catalyst performance. To our surprise, complex **2a** on FRPSG and the nontagged complex **3** on normal silica gel behaved quite similiarly (*Table 1*, *Entries 2* and *8*).

To assess the catalyst leaching, the coupling of phenylboronic acid and *p*-bromomandelic acid was carried out with 0.1 mol-% of **2a** on FRPSG **1** and 0.1 mol-% of **3** on unmodified silica gel. After reaction, the support was filtered off and washed with H_2O. The combined filtrates were evaporated, and the Pd-content was determined by inductively coupled plasma (ICP) MS. For **2a** on FRPSG, the amount of Pd in the crude product was 2.2 ppm, corresponding to 0.8% of the Pd, whereas, for **3** on silica gel, we observed 14.0 ppm in the crude product, corresponding to 7.4% of the Pd.

Despite the low leaching of Pd, the question still remained whether the catalytic process proceeded in a heterogeneous or a homogeneous fashion. To shed more light on this problem, we carried out a three-phase test (*cf. Ley* and co-workers [19]) in which a solid-phase-bound aryl iodide was subjected to the reaction conditions (*Scheme 2*). If the catalyst is truly immobilized, the spatial separation from the iodide prevents any conversion, while a soluble catalyst can reach the substrate by diffusion, and thus, effect conversion. We carried out the experiment with complex **2a** supported on FRPSG **1** in the presence and in the absence of bromomandelic acid as a soluble substrate. Similarly, control experiments were carried out with complex **3** on unmodified silica gel. In all four experiments, over 80% conversion of the solid-phase-bound iodide was observed. These results suggest that the catalyst is operating by a homogeneous mechanism and does not depend on a soluble aryl halide for generation of the active species from the precatalyst.

Scheme 2. *Three-Phase Test: Behavior of a Solid-Phase-Bound Aryl Iodide under* Suzuki *Coupling Conditions.* Upon cleavage from the support, the conversion was determined by HPLC.



The assumption of a homogeneous catalyst is supported further by the finding that the reaction continues after filtration of the reaction mixture and leads to the same conversions (*Fig. 2*). Upon completion of the reaction and cooling to room temperature, the Pd-species are possibly recaptured by the solid phase, which would be in accordance with the low Pd-leaching. Such a 'release and capture' mechanism has been invoked recently for a catalyst based on Pd-containing perovskites [19]. But it is also conceivable that the support acts as a reservoir, and only a small fraction of active

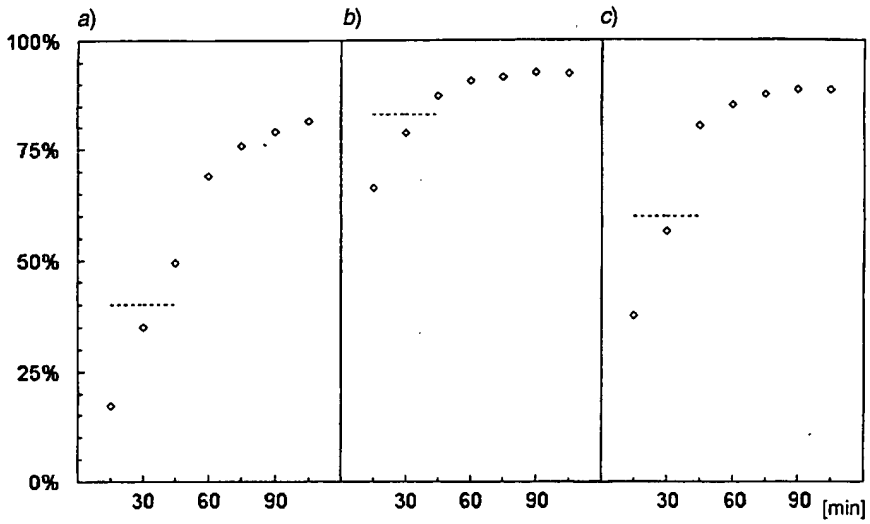


Fig. 2. *Formation of phenylmandelic acid* vs. *reaction time.* Reaction conditions: 0.1 mol-% **2a**/FRPSG, Na_2CO_3, H_2O, 80°, 16 h. *a*) Fresh catalyst, *b*) reused catalyst, *c*) second reuse. The dashed line denotes the filtration of the reaction mixture.

catalyst is released into the solution. That very small catalyst amounts can lead to high conversion, was already shown above (*Table 1, Entry 4*).

Furthermore, Pd-complex **2a** was evaluated in the *Suzuki* coupling of different substrates (see *Scheme 3* and *Table 2*). The reaction proceeded well with a range of H_2O-soluble substrates, and the catalyst could be recycled. Only in the case of 2-bromobenzoic acid, the yield was low and recycling of the catalyst was not successful (*Table 2, Entry 4*). This is probably due to steric hindrance of the *o*-carboxyl group. On the other hand, in the boronic acid, small *o*-substituents were well tolerated, as the comparison of (4-methoxyphenyl)boronic acid (*Table 2, Entries 8* and *9*) and (2-methoxyphenyl)boronic acid (*Table 2, Entries 10* and *11*) shows. In the coupling of 4-bromophenylacetic acid with (4-formylphenyl)boronic acid, less than 5% conversion was observed in the first run (not shown). Upon recycling of the catalyst, slightly increased activity was observed, with 15% conversion of the bromide. With less H_2O-soluble substrates like 4-bromoacetophenone or 4-bromobutylbenzene, no significant consumption of boronic acid could be observed. It is possible that, in these cases, the

Scheme 3. Suzuki *Reactions with Different Substrates in the Presence of 0.1 mol-%* **2a** *on Support* **1**

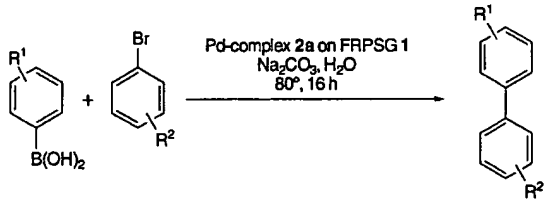


Table 2. Suzuki *Reactions with Different Substrates in the Presence of 0.1 mol-% 2a on Support 1 (Scheme 3)*

Entry	R^1	R^2	Yield [%]
1	H	4-$CH(OH)CO_2H$	100 (94, 93)
2	H	4-CO_2H	100 (97, 93)
3	H	3-CO_2H	99 (93, 90)
4	H	2-CO_2H	30 (6, 8)
5	H	4-CH_2CO_2H	100 (82, 88)
6	H	4-$CONHCH_2CO_2H$	94 (98)
7	H	3-$CONHCH_2CO_2H$	76 (97)
8	4-MeO	4-$CH(OH)CO_2H$	99 (88, 99)
9	4-MeO	4-CH_2CO_2H	89 (99)
10	2-MeO	4-$CH(OH)CO_2H$	98 (99, 99)
11	2-MeO	4-CH_2CO_2H	78 (95)

hydrophobic substrate covers the solid support and mechanically prevents the contact between the solution and the precatalyst.

Conclusions. – In summary, we could demonstrate that perfluoro-tagged Pd-complexes immobilized on FRPSG **1** are useful as precatalysts for the *Suzuki* reaction in H_2O, despite their pronounced hydrophobicity. There is conclusive evidence that the actual catalysis proceeds *via* a homogeneously dissolved Pd-species. H_2O-Soluble substrates were easily converted to the corresponding biphenyls. The supported complexes were separated by simple filtration and could be reused several times. With low catalyst loadings, TONs as high as 200000 were achieved.

Financial support from *Fluka*, Buchs (CH), is gratefully acknowledged.

Experimental Part

General. All reagents and solvents were obtained from either *Fluka* or *Aldrich* and were used without further purification. HPLC: *Agilent-1100* system with binary pump, sample changer, column oven, and diode-array detector. M.p.: *IA9000* apparatus from *Electrothermal Engineering Ltd.*; uncorrected. NMR Spectra: chemical shifts δ in ppm rel. to $SiMe_4$ (= 0 ppm) for ^1H- and rel. to $CHCl_3$ (= 77 ppm) for ^{13}C. MS: *Finnigan MAT8200* (EI), *MAT312* (CI), and *TSQ7000* (ESI) spectrometer; APCI = atmospheric-pressure chemical ionization, ICP = inductively coupled plasma; in *m/z* (rel. %).

Typical Procedure for Recycling Experiments. To FRPSG-supported catalyst (100 mg) under Ar, an aq. stock soln. of the substrates (3 ml, containing 0.3 mmol of 4-bromomandelic acid, 0.33 mmol of phenylboronic acid, and 0.6 mmol of Na_2CO_3) was added. The mixture was shaken at 80° for 16 h. An aliquot (20 µl) of the soln. was withdrawn, and the yield was measured by HPLC analysis. The mixture was cooled to 20° and filtered. The FRPSG was washed with 1M HCl in MeOH/H_2O 11:1 (2 × 1 ml), MeOH (2 × 1 ml), and H_2O (2 × 1 ml). The immobilized catalyst was reused as such in further experiments. All manipulations were carried out automatically (*Automated Synthesis Workstation ASW 2000*, *Chemspeed Ltd.*, Augst, Switzerland). HPLC analysis: *C-18* column (*Zorbax SB*, 3 µm, 4.6 × 50 mm); isocratic eluent H_2O/MeCN/HCOOH 70:30:0.2 (*v/v*); detection at 210 nm; conversions calculated from the ratio of the peak areas of 4-bromomandelic acid and 4-phenylmandelic acid corrected for the extinction coefficients.

General Procedure (G. P.) for Preparative Experiments: 4-Phenylmandelic Acid (= α-Hydroxy[1,1'-biphenyl]-4-acetic Acid): A 13-ml glass reactor was charged with FRPSG-supported catalyst (100 mg), solid 4-bromomandelic acid (69 mg, 0.3 mmol), and phenylboronic acid (40 mg, 0.33 mmol). Under Ar, 2M aq. Na_2CO_3 (3 ml, 0.6 mmol) was added. The mixture was shaken at 80° for 16 h. Aliquots (20 µl) of the soln. were withdrawn at the beginning of the reaction and after 16 h, and the conversion was estimated by HPLC. The mixture was cooled to 20° and filtered. The FRPSG was washed with H_2O (4 × 1 ml). The immobilized catalyst

was reused as such in further experiments. Up to this point, all manipulations were carried out automatically by *Chemspeed ASW 2000*. The aq. product soln. was acidified with conc. HCl soln. (1 ml) and extracted with Et_2O (3 × 5 ml) and the combined extract evaporated to give the product. An anal. sample was crystallized from AcOEt. M.p. 199° ([20]: 202–204°). ^{1}H-NMR ((D$_6$)DMSO, 400 MHz): 7.62–7.66 (*m*, 4 arom. H); 7.50 (*m*(*AA'BB'*), J_{app} = 8.2, 2 arom. H); 7.45 ('*t*', J_{app} = 7.7, 2 arom. H); 7.35 ('*t*', J_{app} = 7.5, 1 arom. H); 5.08 (*s*, CH). ^{13}C-NMR ((D$_6$)DMSO, 100.6 MHz): 174.0; 139.8; 139.5; 139.3; 128.9; 127.4; 127.2; 126.6; 126.4; 72.1. EI-MS: 228 (52, M^+), 183 (100, $[M - CO_2H]^+$), 155 (41).

[1,1'-Biphenyl]-4-carboxylic Acid. According to the *G. P.*, but with a different workup procedure: Upon completion of the reaction, the mixture was filtered and the FRPSG washed with 1M HCl in MeOH/H_2O 11:1 (2 × 1 ml), MeOH (2 × 1 ml), and H_2O (2 × 1 ml). The combined filtrate was diluted with sat. aq. NaCl soln. (30 ml) and extracted with Et_2O (3 × 20 ml). The combined extracts were evaporated to give the product. An anal. sample was crystallized from MeOH. M.p. 223–226° (dec.) ([21]: 226–228°). ^{1}H-NMR ((D$_6$)DMSO, 400 MHz): 8.01 (*m*(*AA'BB'*), J_{app} = 8.2, 2 arom. H); 7.79 (*m*(*AA'BB'*), J_{app} = 8.2, 2 arom. H); 7.72 (*m*(*AA'BB'*), J_{app} = 7.3, 2 arom. H); 7.49 ('*t*', J_{app} = 7.5, 2 arom. H); 7.41 ('*t*', J_{app} = 7.3, 1 arom. H). ^{13}C-NMR ((D$_6$)DMSO, 100.6 MHz): 167.0; 144.2; 139.0; 129.9; 129.6; 129.0; 128.2; 126.9; 126.7. EI-MS : 198 (100, M^+), 181 (63, $[M - OH]^+$).

[1,1'-Biphenyl]-3-carboxylic Acid. According to the *G. P.* M.p. 168° ([22]: 169–170°). ^{1}H-NMR ((D$_6$)DMSO, 400 MHz): 13.0 (br., OH); 8.17 (*t*, *J* = 1.7 Hz, 1 arom. H); 7.89–7.95 (*m*, 2 arom. H); 7.69 (*m*(*AA'BB'*), J_{app} = 7.3, 2 arom. H); 7.59 (*t*, *J* = 7.7, 1 arom. H); 7.49 ('*t*', J_{app} = 7.7, 2 arom. H); 7.40 ('*t*', J_{app} = 7.3, 1 arom. H). ^{13}C-NMR ((D$_6$)DMSO, 100.6 MHz): 167.1; 140.5; 139.2; 131.4; 131.0; 129.3; 129.0; 128.2; 127.8; 127.2; 126.7. EI-MS: 198 (100, M^+), 181 (29, $[M - OH]^+$), 152 (34).

[1,1'Biphenyl]-4-acetic Acid. According to the *G. P.* M.p. 165° ([20]: 161–162°). ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.54–7.59 (*m*, 4 arom. H); 7.42 ('*t*', J_{app} = 8.0, 2 arom. H); 7.31–7.37 (*m*, 3 arom. H); 3.69 (*s*, CH_2). ^{13}C-NMR ($CDCl_3$, 100.6 MHz): 177.4; 140.8; 140.5; 132.4; 129.9; 128.9; 127.5; 127.4; 127.2; 40.7. EI-MS: 212 (53, M^+), 167 (100, $[M - CHO_2]^+$).

4-Phenylhippuric Acid. (= N-*([1,1'-Biphenyl]-4-ylcarbonyl)glycine*). According to the *G. P.*, but extraction with AcOEt instead of Et_2O. M.p. 218–219° (dec.) ([23]: 211°). ^{1}H-NMR ((D$_6$)DMSO, CD_3OD, 500 MHz): 7.94 (*m*(*AA'BB'*), J_{app} = 8.6, 2 arom. H); 7.75 (*m*(*AA'BB'*), J_{app} = 8.6, 2 arom. H); 7.70 (*m*, J_{app} = 8.2, 2 arom. H); 7.46 ('*t*', J_{app} = 7.6, 2 arom. H); 7.38 (*m*, 1 arom. H); 3.95 (*s*, CH_2). ^{13}C-NMR ((D$_6$)DMSO, CD_3OD, 125.7 MHz): 171.6; 166.7; 143.5; 139.6; 132.9; 131.7; 129.3; 128.2; 127.1; 126.8; 41.3. EI-MS: 255 (15, M^+), 211 (51, $[M - CO_2]^+$), 181 (100, $C_{13}H_9O^+$), 152 (44).

3-Phenylhippuric Acid (= N-*([1,1'-Biphenyl]-3-ylcarbonyl)glycine*). According to the *G. P.*, but extraction with AcOEt instead of Et_2O. M.p. 212–213° ([24]: 219°). ^{1}H-NMR (CD_3OD, 500 MHz): 8.12 (*t*, *J* = 1.9, 1 arom. H); 7.83 (*ddd*, *J* = 7.7, 1.8, 1.1, 1 arom. H); 7.80 (*ddd*, *J* = 7.8, 1.9, 1.1, 1 arom. H); 7.65–7.67 (*m*, 2 arom. H); 7.54 (*t*, *J* = 7.8, 1 arom. H); 7.45 ('*t*', J_{app} = 7.9, 2 arom. H); 7.34 ('*t*', J_{app} = 7.4, 1 arom. H); 4.12 (*s*, CH_2). ^{13}C-NMR (CD_3OD, 125.7 MHz): 173.2; 170.4; 142.9; 141.5; 135.7; 131.4; 130.2; 130.0; 128.8; 128.1; 127.2; 127.0; 25.6. EI-MS: 255 (27, M^+), 211 (37, $[M - CO_2]^+$), 181 (100, $C_{13}H_9O^+$), 152 (58).

4-(4-Methoxyphenyl)mandelic Acid (= *α-Hydroxy-4'-methoxy[1,1'-biphenyl]-4-acetic Acid*). According to the *G. P.*, but workup as described above for [1,1'-biphenyl]-4-carboxylic acid. ^{1}H-NMR (CD_3OD, 400 MHz; * = overlapping): 7.55* (*m*(*AA'BB'*), J_{app} = 8.6, 2 arom. H); 7.53* (*m*(*AA'BB'*), J_{app} = 9.0, 2 arom. H); 7.46 (*m*(*AA'BB'*), J_{app} = 8.2, 2 arom. H); 6.97 (*m*(*AA'BB'*), J_{app} = 9.0, 2 arom. H); 5.21 (*s*, CH); 3.81 (*s*, MeO). ^{13}C-NMR (CD_3OD, 100.6 MHz): 174.9; 160.9; 142.2; 138.7; 134.3; 129.0; 127.6; 115.3; 74.1; 55.8. APCI-MS (neg.): 257 (100, $[M - H]^-$), 213 (14, $[M - CO_2H]^-$).

4-(4-Methoxyphenyl)phenylacetic Acid (= *4'-Methoxy[1,1'-biphenyl]-4-acetic Acid*). According to the *G. P.*, but workup as described above for [1,1'-biphenyl]-4-carboxylic acid. ^{1}H-NMR (CD_3OD, 400 MHz): 7.49–7.53 (*m*, 4 arom. H); 7.32 (*m*(*AA'BB'*), J_{app} = 8.2, 2 arom. H); 6.97 (*m*(*AA'BB'*), J_{app} = 9.0, 2 arom. H); 3.81 (*s*, MeO); 3.60 (*s*, CH_2). ^{13}C-NMR (CD_3OD, 100.6 MHz): 176.0; 160.7; 140.7; 134.7; 134.6; 130.8; 128.9; 127.6; 115.3; 55.8; 41.9. EI-MS: 242 (80, M^+), 197 (100, $[M - CO_2H]^+$), 182 (15), 154 (31).

4-(2-Methoxyphenyl)mandelic Acid (= *α-Hydroxy-2'-methoxy[1,1'-biphenyl]-4-acetic Acid*). According to the *G. P.* ^{1}H-NMR (CD_3OD, 400 MHz): 7.44–7.48 (*m*(*AA'BB'*), 4 arom. H); 7.24–7.31 (*m*, 2 arom. H); 7.04 (*d*, *J* = 8.2, 1 arom. H); 6.98 (*t*, *J* = 7.5, 1 arom. H); 5.15 (*s*, *CH*OH); 3.76 (*s*, MeO). ^{13}C-NMR (CD_3OD, 100.6 MHz): 176.4; 158.0; 140.0; 139.4; 131.7; 131.6; 130.5; 129.9; 127.4; 121.9; 112.7; 74.2; 56.0. APCI-MS (neg.): 257 (100, $[M - H]^-$), 213 (44, $[M - CO_2H]^-$).

4-(2-Methoxyphenyl)phenylacetic Acid (= *2'-Methoxy[1,1'-biphenyl]-4-acetic Acid*). According to the *G. P.* ^{1}H-NMR (CD_3OD, 500 MHz; * = overlapped): 7.40 (*m*(*AA'BB'*), J_{app} = 8.5, 2 arom. H); 7.22–7.29* (*m*, 2 arom. H); 7.25* (*m*(*AA'BB'*), J_{app} = 7.8, 2 arom. H); 7.01 (*dd*, *J* = 8.2, 1.0, 1 arom. H); 6.97 (*td*, *J* = 7.5, 1.1,

1 arom. H); 3.73 (*s*, MeO); 3.63 (*s*, CH_2). ^{13}C-NMR (CD_3OD, 125.7 MHz): 175.7; 158.0; 138.8; 134.5; 132.4; 131.6; 130.6; 129.9; 129.7; 121.9; 112.6; 56.0; 41.7. EI-MS: 242 (100, M^+), 197 (94, $[M-CO_2H]^+$), 181(54).

O¹-([1,1'-Biphenyl-4-ylmethyl)glycerol (= 3-([1,1'-Biphenyl]-4-ylmethoxy)propane-1,2-diol). According to the *G. P.*, but extraction with AcOEt instead of Et_2O. ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.55–7.57 (*m*, 4 arom. H); 7.42 (*t*, *J* = 7.77, 2 arom. H); 7.37 (*d*, *J* = 8.2, 2 arom. H); 7.33 ('*t*', *J* = 7.5, 1 arom. H); 4.57 (*s*, ArCH_2); 3.91 (*m*, 1 H); 3.68–3.72 (*m*, 1 H), 3.60–3.64 (*m*, 1 H); 3.52–3.59 (*m*, 2 H); 2.9 (br., 2 OH). ^{13}C-NMR ($CDCl_3$, 125.7 MHz): 140.9; 140.7; 136.7; 128.8; 128.3; 127.4; 127.2; 127.1; 73.3; 71.8; 70.7; 64.1. EI-MS: 258 (7, M^+), 183 (48, $C_{13}H_{11}O^+$); 167 (100, $C_{13}H_{11}^+$), 152 (33, $C_{12}H_8^+$).

Typical Procedure for the Determination of Pd Leaching on Preparation of 4-Phenylmandelic Acid. To supported catalyst (500 mg, 1.5 μmol of Pd-complex **2a** or **3** on either FRPSG or silica gel), an aq. stock soln. of the substrates (15 ml, containing 1.5 mmol of 4-bromomandelic acid, 1.65 mmol of phenylboronic acid, and 3.0 mmol of Na_2CO_3) was added under Ar. The mixture was shaken at 80° for 16 h. The mixture was cooled to r.t. and filtered. The FRPSG was washed with H_2O (4 × 5 ml). The combined filtrate was evaporated, and the Pd-content of the solid residue was determined by ICP-MS (*Solvias*, Basel, Switzerland).

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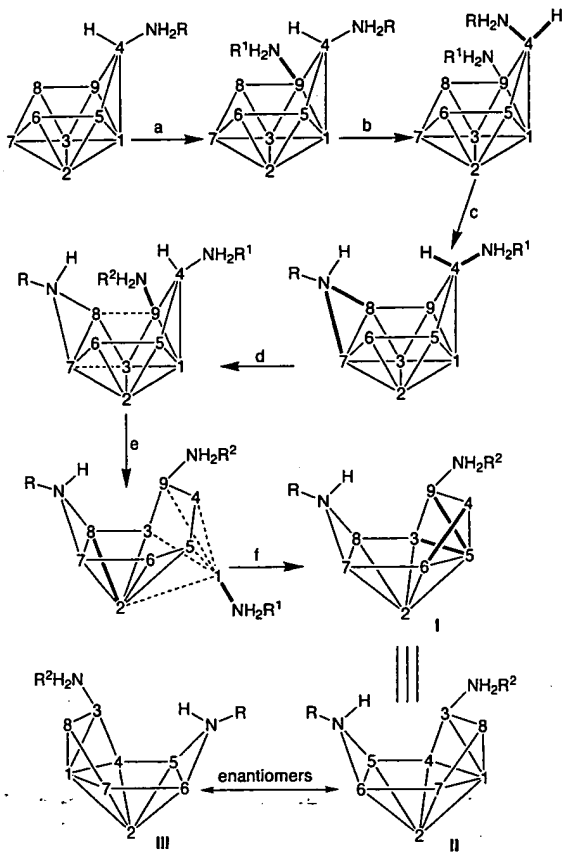
APPENDIX D



Scheme 2. Mechanistic pathway of the conversion of the nonaborane cluster into the azanonaborane cluster (**I** IUPAC numbering of the B_9 cluster, **II** and **III** IUPAC numbering of the B_8N cluster).[10] Bold lines: new bonds; dashed lines: bonds to be broken.

experiments with the Et- and Br-substituted clusters) and B^3 (concluded from the experiments with a tetradeuterated cluster). Computed ^{11}B NMR chemical shifts, supported by 2D-^{11}B COSY and ^1H CW ^{11}B NMR spectra showed the Et group to be connected to B^6, opposite to the *exo*-amino ligand at B^3 in the B_8N cluster **9**; the data further indicated that the Br atom at B^6 in the B_9 cluster **5** is located at B^7 and not at B^4 in the B_8N cluster **11**. The fate of the boron atoms B^5, B^8, and B^9 has not been clarified, but the proposed mechanism would require only a minimal rearrangement of the bonds (one DSD rearrangement and the closing of the cluster after the loss of B^1). The loss of B^1, which is *not* part of the open face, is surprising. Quantum-mechanical computations might give indications about the feasibility of the proposed pathway, the relative stability of the proposed intermediates, the origin of the H atoms which leave together with B^1, and the rearrangement of the other H atoms.

Experimental Section

1, 8–12: Isopropylamine (0.1 g, 1.74 mmol) was added to a solution of $(Me_2S)B_9H_{13}$ in dry benzene (10 mL, 0.1 g) at room temperature. The mixture was heated to reflux for 3 h. All volatile components were removed under vacuum and the resulting substance was recrystallized from ethanol:water (1:1). Compounds **8** and **9** were purified by TLC by using CH_2Cl_2 as eluent ($R_f = 0.31$). For further purification the substance was dissolved in $CHCl_3$:hexane (1:3) at −20 °C. The solution was filtered and the resulting filtrate was evaporated to dryness to yield the purified product. **1** (DCI): *m/z* (%) 214 (95) [M^+]; **8, 9** MS (EI, 750 eV, 200 °C): *m/z* (%) 242 (24) [M^+]; **10, 11**, (EI, 750 eV, 200 °C): *m/z* (%) 293 (18) [M^+]; **12** (FAB^+): *m/z* (%) 217 (100) [M^+].

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Fluorous Biphasic Catalysis without Perfluorinated Solvents: Application to Pd-Mediated Suzuki and Sonogashira Couplings**

Carl Christoph Tzschucke, Christian Markert, Heiko Glatz, and Willi Bannwarth*

In catalytic reactions easy handling of the catalyst together with its straightforward recovery and possible reuse remain an important topic. A widespread solution to reach these goals is the application of immobilized catalysts. Immobilization can be achieved by covalent attachment to organic polymers or inorganic support materials.[1] Alternatively, catalysts can be adsorbed on silica gel[2–4] or on reversed-phase silica gel.[5] In some cases the immobilization has a beneficial effect on the catalyst's stability.[6,7] One profound advantage of such supported catalysts is the easy separation from the reaction

[*] Prof. Dr. W. Bannwarth, Dipl.-Chem. C. C. Tzschucke, Dipl.-Chem. C. Markert, Dipl.-Chem. H. Glatz
Institut für Organische Chemie und Biochemie
Albert-Ludwigs-Universität Freiburg
Albertstrasse 21, 79104 Freiburg (Germany)
Fax: (+49) 761-203-8705
E-mail: willi.bannwarth@organik.chemie.uni-freiburg.de

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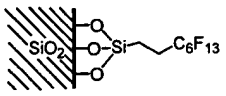
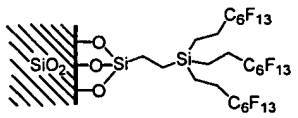
product by filtration or decantation. Ideally, without further purification, there should be little or no contamination of the product with transition metals, which is important when the substances are to be tested in biological assays. A further aspect is the straightforward recovery and reuse of the catalyst. Generally, simplification of workup protocols and handling of small amounts of catalysts is especially important in multiparallel and automated synthesis in combinatorial chemistry.[8,9]

Biphasic systems comprising perfluoro-tagged catalysts, which can be extracted out of organic products with fluorous solvents, have emerged as alternative tools for the separation, recovery, and reuse of catalysts as well as for simplified product isolation.[10–15] This method, known as fluorous biphasic catalysis (FBC), has been applied to numerous catalytic reactions.[8,10,16–31] Although perfluorinated solvents have certain advantages, they are expensive and environmentally persistent.[32] Thus, it would be beneficial to perform separation and recovery of perfluoro-tagged catalysts without recourse to a perfluorinated solvent as a second liquid phase. Recently, the thermomorphic solution behavior of a fluorous phosphane was utilized in this context.[33] While fluorous reversed-phase silica gel (FRPSG) has found application as the stationary phase for chromatographic separation of perfluoro-tagged compounds,[34,35] it has not been used to support catalysts.

Our rational was to substitute fluorous solvents by FRPSG, thus gaining easy separation and at the same time retaining the advantages of soluble perfluoro-tagged catalysts. As a first example for this strategy, we report on the immobilization of perfluoro-tagged bis(triphenylphosphane)palladium complexes on FRPSG and their successful application to the Suzuki and Sonogashira C–C coupling reactions without need for a fluorous solvent.



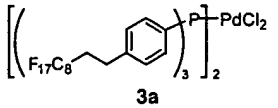
1



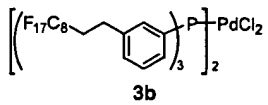
2

The fluorous solid supports **1** and **2** were prepared by adapted standard procedures.[36,37] Palladium complexes **3a–c** were synthesized by our established procedures.[30]

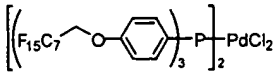
To immobilize the complexes, FRPSG was added to a solution of the respective complex in diethyl ether and hexafluorobenzene and the solvent was evaporated. The immobilized precatalyst is an air-stable, free-flowing powder. For ease of handling, especially in separations, FRPSG with a coarse grain (100–300 μm particle size) was used. Silica gels **1** containing 0.1, 1.0, 10, and 100 mg complex per g FRPSG, respectively, were evaluated in the Suzuki cross-coupling of phenylboronic acid and *para*-nitrobromobenzene and in the Sonogashira coupling of phenylacetylene and *para*-nitrobromobenzene (Table 1).



3a



3b



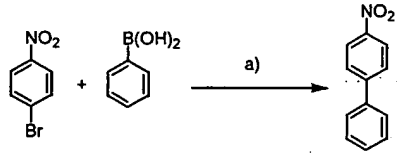
3c

Table 1. Suzuki and Sonogashira reactions with different amounts of complex **3a**.

Entry	Catalyst loading of FRPSG [mg g^{-1}]	Catalyst loading [mol%]	Yield [%][a]
Suzuki			
1	100	1.5	>98 (>98, 92)
2	10	0.1	>98 (>98)
3	1	0.01	>98 (>98)
4	0.1	0.001	86 (45)
Sonogashira			
5	100	2	>98 (97, 71)
6	10	0.2	>98 (30, 0)
7	1	0.02	22 (0)
8	0.1	0.002	11 (0)

[a] The yields in parentheses are for the second (and third) runs with the same catalyst.

In the Suzuki reaction (Scheme 1) complete conversions were obtained with catalyst loadings down to 0.01 mol% and the catalyst could be recycled (Table 1, entries 1–3). With 0.001 mol% of catalyst, the yield in the first run was 86% and dropped to 45% in the second run (Table 1, entry 4). This corresponds to a cumulated turnover number (TON) of 131000.



Scheme 1. Suzuki reactions performed with **3a–c** immobilized on support **1** as catalysts. a) 0.001–1.5 mol% catalyst, DME, 2M aq. Na_2CO_3, 80°C.

Further experiments were performed by using 10 mg Pd complex per g FRPSG, and a catalyst loading of 0.1 mol%. The three different complexes **3a–c** were used in the coupling of *para*-nitrobromobenzene and phenylboronic acid. Complexes **3a** and **3b** both have an ethylene spacer separating the perfluoroalkyl chain and the phenyl ring, the perfluoro tag is attached to the *para* or *meta* position, respectively. In complex **3c** an OCH_2 spacer is used. Earlier experiments had shown that spacers between the perfluoroalkyl chain and the aromatic ring are advantageous for the stability of the catalysts.[38]

All three catalysts gave complete conversions and could be recycled without significant decrease of activity (Table 2). Catalyst leaching was assessed for the coupling of *para*-nitrobromobenzene and phenylboronic acid with 0.1 mol% of complex **3a**. Using support **1**, a Pd content of 5.4 ppm in the crude organic product was determined by inductively coupled

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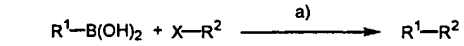
Table 2. Suzuki reactions with complexes **3a–c** immobilized on **1** (see Scheme 1).

Entry	Pd complex	Yield [%][a]
1	**3a**	> 98 (93, 93, 93)
2	**3b**	96 (98, 93, 91)
3	**3c**	> 98 (96, 95, 95)

[a] The yields in parentheses are for the second (third, and fourth) runs with the same catalyst.

plasma mass spectrometry (ICP-MS),[39] which corresponds to 1.8% of the total Pd. In the inorganic residue, which consists mainly of Na_2CO_3, 0.2 ppm of Pd was found, which corresponds to less than 0.1% of the Pd. Thus, less than 1.9% of the catalyst was washed off from FRPSG **1**. In an identical experiment using support **2** a Pd leaching of less than 1.6% was determined. Accordingly, the nature of the fluorous solid support seems to influence the leaching only marginally.

The catalyst **3a** on support **1** was tested with a number of different substrates (Scheme 2, Table 3). Yields were generally high for electron-deficient aryl bromides (Table 3,



Scheme 2. Suzuki reactions with different substrates performed with **3a** immobilized on support **1** as catalyst. X = Br, I. a) 0.1 mol% catalyst, DME, 2 M aq. Na_2CO_3, 80°C, 15 h.

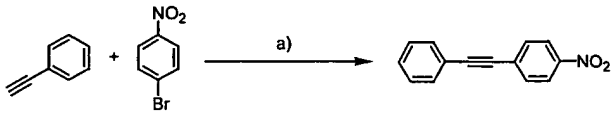
Table 3. Suzuki reactions with different substrates, using 0.1 mol% **3a** on support **1** (see Scheme 2).

Entry	R^1	R^2	Yield [%][a]
1	Ph	4-NO_2-C_6H_4	95 (97, 97)
2	Ph	4-CH_3CO-C_6H_4	> 98 (85, 14)
3	Ph	4-EtOOC-C_6H_4	93 (69, 4)
4	Ph	2-naphthyl	82 (17)
5	Ph	3,4-$F_2C_6H_3$	78 (6, 0)
6	Ph	3,4,5-$F_3C_6H_2$	83 (34, 2)
7	Ph	4-MeO-C_6H_4	48 (2)
8[b]	Ph	4-MeO-C_6H_4	76, (75, 52)
9[c]	Ph	4-MeO-C_6H_4	70, (10, 0)
10[d]	Ph	4-MeO-C_6H_4	73 (4, 0)
11	4-MeO-C_6H_4	4-NO_2-C_6H_4	94 (97, 94)
12	4-MeO-C_6H_4	4-CN-C_6H_4	94 (97, > 98)
13	4-MeO-C_6H_4	4-CH_3CO-C_6H_4	85 (> 98, 29)
14	4-MeO-C_6H_4	4-EtOOC-C_6H_4	72 (56, 19)
15	3-thienyl	4-NO_2-C_6H_4	89 (0)
16	3-thienyl	4-CH_3CO-C_6H_4	61 (0)
17	Cy	4-NO_2-C_6H_4	0 (0)
18	Cy	4-CH_3CO-C_6H_4	0 (0)

[a] The yields in parentheses are for the second (and third) runs with the same catalyst. [b] 4-Iodoanisole was used instead of 4-bromoanisole. [c] 0.3 mol% **3a** was used. [d] 0.2 mol% of the corresponding phosphane was added.

entries 1–6, and 11–15) and for aryl iodides (Table 3, entry 8). For electron-rich *para*-bromoanisole only 48% conversion was achieved (Table 3, entry 7), but higher conversions were obtained with either higher catalyst loading (Table 3, entry 9) or additional phosphane ligand (Table 3, entry 10). Recycling was successful for very reactive substrates (Table 3, entries 1, 11, and 12). For all other substrates a significant decrease of catalyst activity was observed, the decrease being the greater, the less reactive the halide was. With 3-thienylboronic acid high conversions were obtained in the first run, but no conversion was found with recycled catalyst and only the aryl bromide was recovered (Table 3, entries 15 and 16). This complete loss of activity might be due to catalyst poisening by the thiophene. With cyclohexylboronic acid no conversion was observed (Table 3, entries 17 and 18).

In the Sonogashira reaction (Scheme 3) with 2 mol% catalyst high yields were obtained for three successive experiments (Table 1, entry 5). With 0.2 mol% catalyst conversion was still complete, but the yield dropped significantly when the catalyst was reused (Table 1, entry 6). With lower catalyst loadings, conversions were not complete within 14 h and the recovered FRPSG showed no catalytic activity (Table 1, entries 7 and 8).



Scheme 3. Sonogashira reactions performed with complex **3a** immobilized on support **1** as catalyst. a) 0.002–2 mol% catalyst, CuI, DME, nBu_2NH, 100°C, 14 h.

In summary, we could demonstrate the immobilization of perfluoro-tagged palladium catalysts on FRPSG, and their use for Suzuki and Sonogashira cross-coupling reactions. The catalysts showed activities comparable to those found in liquid–liquid FBC. The catalysts were separated from the product by simple decantation. Leaching was as low as 1.9% and 1.6% for **1** and **2**, respectively, and the recovered catalyst could be reused in several instances. Because of the dilution of the catalyst with FRPSG, very small amounts of catalysts could be easily and precisely handled. In contrast to conventional FBC approaches, no fluorous solvent was needed for the reaction and the isolation and recovery of the catalyst. An advantage of our strategy compared to conventional covalent catalyst immobilization is that the same support can be used for different catalysts, without the need for a separate linker unit. Before attachment, the catalyst can be characterized by usual methods. It is also conceivable to adjust the reaction conditions in such a way that the catalyst is detached from the FRPSG during the reaction and re-attached during workup. Further investigations to extend this immobilization strategy to other catalytic systems are currently underway.

Experimental Section

General procedure for Suzuki cross-coupling reactions: A 50 mL Schlenk tube was charged with FRPSG supported catalyst (100 mg), evacuated, and refilled with argon (3×). Stock solutions of the aryl halide (0.3 M in dimethoxyethane (DME), 1.0 mL, 0.3 mmol), the boronic acid (0.33 M in DME (with 4-methoxyphenylboronic acid methanol was used instead), 1.0 mL, 0.33 mmol) and Na_2CO_3 (2 M in water, 1.0 mL, 2.0 mmol) were added. The tube was sealed with a screw cap and shaken at 80°C for 15 h. The reaction mixture was cooled to 0°C and the liquid phase was removed under argon with a pipette. The FRPSG was washed with DME (2 × 2 mL), water (2 × 2 mL), and DME (2 × 2 mL). The combined liquid phases were diluted with water (40 mL) and brine (20 mL) and were extracted with *tert*-butyl methyl ether (3 × 20 mL). The combined extracts were concentrated in vacuo, the residue was take up in diethyl ether (2 mL), put on a plug of

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neutral alumina (3 mL, activity 2–3) and eluted with diethyl ether (~14 mL). Evaporation of the solvent gave the product. Yields were determined by ^{1}H NMR integration against a known amount of 1,2-dibromoethane. The immobilized catalyst was reused as such in further experiments.

Determination of catalyst leaching: A 100 mL Schlenk flask was charged with FRPSG supported catalyst (500 mg, 10 mg Pd complex per g FRPSG, 1.48 μmol), 4-bromonitrobenzene (303 mg, 1.50 mmol), and phenylboronic acid (205 mg, 1.68 mmol), evacuated and refilled with argon (3×). DME (10 mL) and Na_2CO_3 (2M in water, 5.0 mL, 10.0 mmol) were added. The flask was shaken under argon at 80°C for 15 h, and then the reaction mixture was cooled to room temperature and filtered. The residue was washed with DME (2×10 mL), water (2×10 mL), and again with DME (2×10 mL), and the organic and aqueous filtrates were collected separately. The solvents were removed in vacuo, the resulting solids were powdered, and the Pd content determined by ICP-MS.

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9,9-Dilithiofluorene: The First Crystal-Structure Analysis of an α,α-Dilithiated Hydrocarbon**

Gerald Linti,* Alexander Rodig, and Hans Pritzkow

Lithiated hydrocarbons are one of the most important classes of compounds in organoelement chemistry. Many of these compounds have been structurally investigated in solution and the crystalline state, as well;[1–3] di- and oligometallated species earned special interest.[4,5] Dilithiomethane is mentioned as one example here, it is available from the thermolysis of lithium methanide[6,7] and used in many synthetic procedures. A series of oligomeric structures of lithium methanide was investigated with quantum-chemical methods, in which carbon atoms take the coordination number six.[8] In monomeric dilithiomethane the planar coordination of the carbon atom is only less stable than the tetrahedral coordination of the carbon atom by 71 kJ mol^{-1}.[9,10] However, the final structure in solution and of the solid state has not been determined.[11,12] Several substituted derivatives, such as Me_3CCHLi_2, $Me_3SiCHLi_2$,[13] and the title compound 9,9-Dilithiofluorene,[14] have been synthesized, but their structures are not known. It was possible to solve the crystal structures of heteroatom substituted derivatives, such as $PhS(O)(NMe)CLi_2Ph$,[15] $(Me_3SiNPPh_2)_2CLi_2$,[16,17] $(MeO)_2P(O)CLi_2SiMe_3$ (as aggregate with dimethylamide),[18] and $PhSO_2CLi_2(SiMe_3)$,[19] where Li–O and Li–N bonds dominate the structures. The anion $(CHPMe_2NSiMe_3)^{2-}$ together with $BuMe_2SiO^-$ forms the backbone of a Li_{14} cluster.[20] $[\{(Me_3Si)_2CH\}_6Al_2CH_2Li_2]$ was considered as a R_3Al-adduct to CH_2Li_2.[21] Herein, we describe the crystal structure of the 9,9-dilithiofluorene complex **2** [Eq. (1)].

[*] Prof. Dr. G. Linti, Dr. A. Rodig, Dr. H. Pritzkow
Anorganisch-Chemisches Institut
Universität Heidelberg
Im Neuenheimer Feld 270, 69120 Heidelberg (Germany)
Fax: (+49) 6221-54-6617
E-mail: gerald.linti@urz.uni-heidelberg.de

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APPENDIX E

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Thermoselective phase property of silica tethered with fluorinated chains for controlled 'release' and 'capture' of catalytic fluorous tin species

Peter M. Jenkins, Andrew M. Steele, Shik Chi Tsang *

Department of Chemistry, Surface and Catalysis Research Centre, University of Reading, Whiteknights, Reading RG6 6AD, UK

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Abstract

The temperature dependent mixing of organic and fluorous phases is one of the key principals of fluorous biphasic systems (FBS). Given the high cost of the perfluorous solvents and their impacts to the environment, it is apparent that elimination of these solvents in bulk quantity in the FBS is advantageous. We report for the first time, the surface coverage of silica with a fluorous solvent like material that traps (at ambient temperatures) and releases (at elevated temperatures) a fluorous tin bromide in organic solvent. Here, we demonstrate the catalytic utilisation of this species for the hydrocyclisation of 6-bromo-1-hexene with $NaBH_4$.
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1. Introduction

The unusual phase behaviour of liquid fluorocarbons forms the basis of fluorous biphasic systems (FBS) [1,2] for the recent advancements in separation technology. Perfluorocarbons are extremely non-polar and have low intermolecular forces [3], especially perfluorinated alkanes, ethers, and tertiary amines, these properties can induce total immiscibility with organic solvents at ambient temperatures but complete mixing upon thermal excitation. Hence, reagents or catalysts tagged with fluorous moieties can facilitate homogeneous phase reactions in combination with liquid phase separation of the fluorous-tagged species into the perfluorous solvent upon cooling induced phase separation. Recently, this technology has been elegantly demonstrated for tin mediated reactions [4,5] since separation of the toxic tin species from product(s) is of a great industrial demand [6,7]. A fundamental question is whether the unusual intermolecular forces between fluorous solvent molecules themselves, and with organic solvent molecules, leading to changes in solvent miscibility (liquid–liquid) upon temperature modulation, can be realised using solid supports with chemically tethered fluorous chains (solid–liquid). It is noted that despite the cost of using bulk perfluorous solvents (normally very expensive), their

* Corresponding author. Tel.: +44-118-9316346; fax: +44-118-9316632.
E-mail address: s.c.e.tsang@reading.ac.uk (S.C. Tsang).

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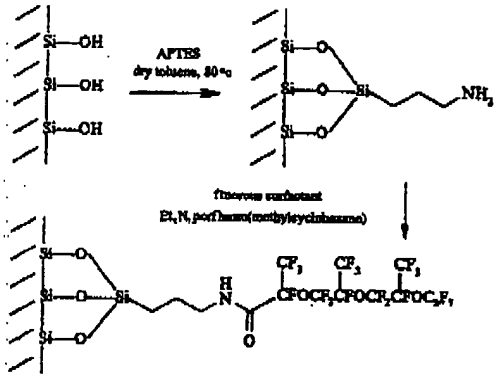
recovery on an industrial scale, and their environmental impacts (known for ozone depletion, greenhouse warming and health and safety issues with product contamination [8]) will be important issues should the FBS become commercially applicable. It is noted that Gladysz and co-workers [9] have recently employed a thermal means without the use of perfluorous solvent for the separation of fluorous species from conventional solvent. We have attempted an alternative approach by replacing the bulk perfluorous solvent with a fluorophilic solid for controlled 'release' and 'capture' of catalytic species immobilised on its surface, via tethered with fluorous chains. Here, we report a fluorous tin bromide immobilised on fluorous silica at mild temperature. At elevated temperatures (60 °C) the fluorous tin is directly released from the modified silica to the organic solvent, 1-butanol in the complete absence of perfluorous solvents. Also, in the presence of a hydrogen source such as $NaBH_4$ the free form of the fluorous tin species catalytically participates in the hydrocyclisation of 6-bromo-1-hexene to methylcyclopentane selectively. Thus, we demonstrate, *for the first time*, that the concept of controlled 'release' and 'recapture' concept of using solid-phase FBS when combined with a catalytic cycle could further enhance tin atom efficiency and its separation from product(s) for hydrogenation reactions. This has significant advantages over the conventional and environmentally unfriendly approach using stoichiometric amounts of tributyltin hydride reagent [6]. It is noted that the general concept of controlled release and capture of catalytic species has been demonstrated as a feasible approach to certain types catalysis. Ion exchange resins [10] with an appropriately chosen transition metal species has been reported for carbonylation reactions. The Heck reaction has also been demonstrated to undergo reversible Pd metal leaching [11].

2. Experimental

2.1. Synthesis

Tris (2-perfluorohexylethyl) tin bromide was prepared as previously described in the literature [4]. The fluorous surface silica was prepared by treating UHPV silica with dilute nitric acid and calcined to increase the number of surface –OH groups, 3-aminopropyltriethoxysilane (APTES) was then grafted to the surface giving the silica NH_2 surface functionality. Finally, perfluoro-(2,5,8-trimethyl-3,6,9-trioxadodecanoyl) fluoride (60% fluorine content by weight) was reacted with this support material yielding the fluorous surface silica upon elimination of HF gas (Scheme 1). Detailed synthesis, surface coverage and characterisation can be found in the supporting material.



Scheme 1. Fluorous silica synthesis.

As seen from Scheme 1, the fluorous silica contains on its surface chemically tethered fluorous chains, these are designed to act similarly to a thin film of perfluorinated solvent. These chains contain in their backbone, ether links that enable the chains to mix well with organic solvents at elevated temperatures.

2.2. Catalysis

Catalytic hydrocylisation of 6-bromo-1-hexene to methylcyclopentane, MCP using our novel system is described. The reaction was performed in 1-butanol with $NaBH_4$ as the hydrogen source. A small catalytic quantity of fluorous tin bromide species released from the solid is converted to the corresponding fluorous tin hydride, which has previously been shown to have comparable activity and selectivity in catalytic hydrogenations. Thus, these reactions were therefore studied in the

Table 1
Retention of fluorous tin bromide on fluorous silica and estimated partition constants

Temperature in °C	0	20	60
Mass of fluorous tin bromide in mg (total mass in system)	4.76 (8.45)	4.04 (9.00)	1.09 (7.99)
Estimated partition constants	$K_{0°C} = 115$	$K_{20°C} = 78$	$K_{60°C} = 12$

presence, and in the absence of fluorous surface modified silica, see Table 2.

3. Results and discussion

3.1. Release and capture

The fluorous surface silica is clearly demonstrated to be 'fluorophilic' by its propensity to extract perfluoromethylcyclohexane, PFMCH (76% fluorine content), from 1-butanol (Fig. 1). The synthesised fluorous tin bromide (60% fluorine content) was also extracted from 1-butanol, at temperatures of 0, 20 and 60 °C, with extractions 56%, 45% and 14% of the total mass of fluorous tin bromide in the system. We observed that 77% of this trapped fluorous tin bromide at 0 °C was released at an elevated temperature of 60 °C, see Table 1.

Experiment. 600 μl 1-butanol, 14 μl PFMCH, 6 μl *n*-decane (internal standard). Aliquots of fluorous silica were made, and data were obtained from 2 μl samples by GC (Perkin Elmer 8500. Run conditions, Start $T = 50$ °C, iso time 1 = 5 min, Ramp rate = 25 °C min^{-1}, Stop $T = 250$ °C, iso time 2 = 0.5 min).

It is evident that the extraction depends on concentration of fluorous species, volume of solvent, mass of fluorous silica and temperature used.

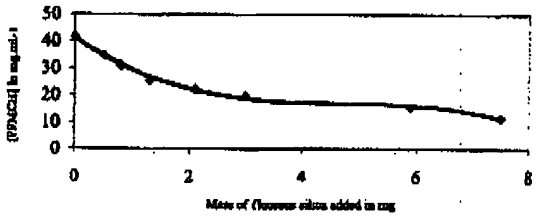


Fig. 1. Extraction of a perfluorous solvent (PFMCH) from 1-butanol.

The fluorous overlayer is believed to act as a chemically tethered 'solvent' surrounded with bulk organic solvent molecules, whereupon the fluorous-tagged species is partitioned. There is only a very limited volume on the surface of the silica for the tethered fluorous chains since there cannot be more than a monolayer coverage though surface aggregation of the chains may be possible. The volume per gram of the composite solid can be roughly calculated from the difference in the observed pore size values before and after the overlayer immobilisation, and is calculated to be 0.25 cm^{-3} g^{-1}. The average pore size diameter in UHPV silica was observed to be 50 Å, after modification, the average pore diameter had reduced to 40 Å. A theoretical model calculation (see supporting material below) based on our estimations of the average thickness of this attached film agrees well with this value. Hence, partition constants of the fluorous tin bromide between the fluorous silica and the 1-butanol solvent may be estimated (Table 1). Without taking the values too literally the obtained partition constants (solid–liquid systems) are comparable to those measured by Curran et al. [4] for the fluorous tin hydride (64% fluorine content) using liquid–liquid systems in FC-72 (perfluorohexane, 78% fluorine)/C_6H_6 and in FC-72/CH_3CN at ambient temperature. Although the partition coefficient depends on structure, the general guide is that the fluorous species will preferentially 'dissolve' into the fluorous solvent if the fluorine contents of both the species and solvent are high. Horváth [1] and Curran et al. [4] suggested 60% fluorine content in both species and solvent would partition well for FBS catalysis applications. Our high values obtained in the thin fluorous layer on the silica may therefore serve the purpose.

The controlled 'release' and 'capture' concept is clearly demonstrated by the ambient temperature trapping of fluorous tin bromide from 1-butanol,

accompanied with its release to 1-butanol at 60 °C, see Table 1. It is noted that the decrease in trapped fluorous tin species at elevated temperatures, corresponding to an increase in the concentration of free species in the organic phase, clearly suggests weakening of intermolecular forces between the fluorous chains (decrease in partition constants versus temperature, Table 1).

Experimental procedure. 10 mg fluorous tin bromide was added to 10 ml 1-butanol and a 1 ml aliquot removed for UV–Vis analysis. 375 mg fluorous silica was added at 20 °C and a further 1 ml aliquot removed for UV–Vis analysis. The remaining 8 ml was cooled to 0 °C and 1 ml removed for analysis. 77% of the trapped fluorous tin was released at 60 °C. Samples for UV–Vis analysis were diluted from 1 to 3 ml with 1-butanol, and the absorbance was recorded at 210 nm with a UVIKON 860 spectrometer.

3.2. Catalysis

The activity and selectivity of fluorous tin species is observed to be very similar to that of results achieved using stiochiometric Bu_3SnH[4] giving mainly MCP (>95%) with a very small amount to 1-hexene and 1-cyclohexane as trace by-products (Table 2). The yields of the fluorous tin species obtained in the presence of the fluorous silica were slightly lower than those in the absence of silica, indicating that some trapped species (refer to Table 1) may be inactive or have a much decreased reaction rate in the catalytic cycle. At 60 °C, 23% of the tin species was still trapped on the solid (Table 1) and a 17% decrease in activity was recorded, a higher temperature is therefore required to release all of the tin species. It is particularly noted that the catalytic activity measured in the presence or absence of fluorous silica both reached a constant value at a very short time consistent with the fast radical hydrogenation reaction (<30 min) and the data remained virtually unchanged for 48 h (completion of results was ensured). As a result, leaching of the catalyst precursor (fluorous bromide) from the fluorous silica seemed not playing an important role. Thus, it is attributed that the catalysis observed is primarily due to the activity of the remaining free form fluorous tin species (converted to active form of fluorous tin hydride) in solution and the loss in activity with fluorous silica compared to the result without the silica corresponds well to the amounts of trapped fluorous tin species within the silica (as indicated in the fluorous tin bromide uptake experiment in Table 1). It is noted that an assumption has been taken that the interactions of the fluorous tin moiety with the fluorous surface silica is mainly via the fluorous chains, the presence of bromide or hydride at the tin center, is not considered to be significant on its fluorophilicity.

Table 2
Hydrocyclisation of 6-bromo-1-hexene to MCP in the presence fluorous silica

Solvent	Fluorous silica	MCP yield (%)	Total turnover no. (h^{-1})
1-Butanol	Yes	51	0.78
1-Butanol	No	62	0.96

In the presence of fluorous silica; 200 mg fluorous silica, 0.10 mmol fluorous tin bromide, 10 ml 1-butanol, 0.20 g $NaBH_4$, 0.91 g 6-bromo-1-hexene, 60 °C for 48 h. In the absence of fluorous silca; 0.10 mmol fluorous tin bromide, 10 ml 1-butanol, 0.20 g $NaBH_4$, 0.91 g 6-bromo-1-hexene, 60 °C for 48 h. Results analysed by GC (Perkin Elmer 8500. Run conditions, 0.2 μl injections. Start $T = 40$ °C, Ramp rate = 5 °C min^{-1}–60 °C, then Ramp at 20 °C min^{-1}, Stop $T = 200$ °C).

4. Conclusion

We show that tin atom efficiency has been improved via its catalytic utilisation (compared to the current stiochiometric approach) and thus less fluorous tin species is required. Although at this stage the efficiency of the silica tethered fluorous chains for trapping and release of soluble fluorous tin species to and from organic solvent at different temperatures may still need to improve (in order to fully demonstrate the technical feasibility) the novel idea of a controlled 'release' and 'capture' type mechanism of the fluorous-tagged tin catalyst species is now demonstrated. As far as we are aware, this is a new approach to facilitate separation of toxic tin from product(s). Elimination of

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the need for a bulk perfluorinated solvent is an important step towards making fluorous tin hydrides an industrially viable technology for the futures green organic synthesis requirements. In radical chemistry, the use of low concentrations of tin hydride to conduct slow radical reactions such as cyclisations is common, this can be done by using either low stationary concentrations or syringe pump addition [4]. Our results indicate that fluorophilic solid may provide a way to control concentrations of fluorous tin reagents in an organic phase simply by modulating the temperature for the release or uptake of the regent thereupon. It is documented that fluorous hydrocarbon reverse-phase silica gel can retain both light fluorous species and heavy fluorine-rich species (require fluorinated co-solvent to release) hence subsequent solid–liquid extraction procedures can be used for fluorous species separation from product [12]. Our novel fluorous silica is capable of direct extraction via releasing and recapturing heavily fluorinated molecules (>60% fluorine content) to and from organic solvent (which is essential for controlled release and capture catalysis with no significant loss of expensive fluorous catalyst). Additionally this is without the use of a bulk perfluorous solvent phase simply by temperature activation. Thus, thermo-selective phase behaviour of the tethered fluorous chains is somewhat akin to the fluorous solvent (unusual intermolecular interactions), but possibly with some degree of control via altering its structure and surface coverage. Thus, the concept of using controlled 'release' and 'capture mechanism in catalysis via fluorine chemistry could be utilised without sequential separation/washing stages for a wide range of catalytic reactions. Porous solids with fluorous overlayers could be used as a novel carrier for fluorous homogeneous species by providing a 'green' process with in situ separation and purification.

5. Supporting material

5.1. Fluorous silica, synthesis

Ultra High Pore Volume (UHPV) silica (5.01 g) was stirred for 30 min in nitric acid (2 cm^3 of 69% conc. nitric acid in 30 cm^3 water), this was filtered and washed with distilled water (4 × 20 cm^3). The silica was then placed in a Schlenk flask at (120 °C) overnight before being placed on a vacuum line and heated to 150 °C for 4 h. In a glove box, dry toluene (20 cm^3) and triethylamine (Et_3N) (4 cm^3) were then added to 4.01 g of this silica. This was left for 30 min before dry toluene (30 cm^3) and 3-aminopropyltriethoxysilane (7 cm^3) were added. The reaction was warmed to boiling point (bpt of Et_3N) for 10 min and left to stand for about 64 h. The silica was filtered, washed with DCM (20 cm^3) and placed in a Soxhlet extractor for 24 h with 1:1 DCM:diethyl ether. This was then filtered and dried in a vacuum oven at 80 °C overnight to give 4.42 g of the NH_2 surface functionality silica. Perfluoromethylcyclohexane (PFMCH) (30 cm^3, degassed) was added followed by perfluoro-(2,5,8-trimethyl-3,6,9-trioxadodecanoyl) fluoride (9.03 g) to 1.94 g of NH_2 surface silica. To this, triethylamine (Et_3N) (1.85 g) was added and the solution heated under reflux for 28 h. The resulting brown silica was washed in a Soxhlet extractor with 1:1 acetone:ether for 4 h followed by 1:1 DCM:ethanol for 3 h and water for 1 h. This gave the brown/orange fluorous surfactant modified silica.

5.2. Fluorous silica, characterisation

A nitrogen absorption isotherm of the silica revealed that the surface area is 244 $m^2\ g^{-1}$. TGA revealed that around 27% of the total mass of the silica was lost between 250 and 450 °C. This was taken as sufficient evidence that the surfactant modification had occurred successfully. Based on the assumption of 4 OH groups nm^{-1} and a surface area of 250 $m^2\ g^{-1}$, the surface coverage with surfactant is 70%.

5.3. Surface volume of overlayer

The volume of the fluorous overlayer on the silica was calculated by the following: the depth of the chains are assumed to be the length of the bonds along the backbone, 5 × C–C + 6 × C–O + 1 × C–F, and is a distance of 1.77 nm. The length of the chains attached to the tin are calculated to be 1.06 nm. Hence only one fluorous tin molecule

in depth can dissolve into the chains attached to the silica, and so the volume on the surface corresponds to the volume occupied by a monolayer of fluorous tin. When calculated, based on a surface area of 250 m^2 g^{-1}, the volume is 0.25 ml g^{-1}.

Acknowledgements

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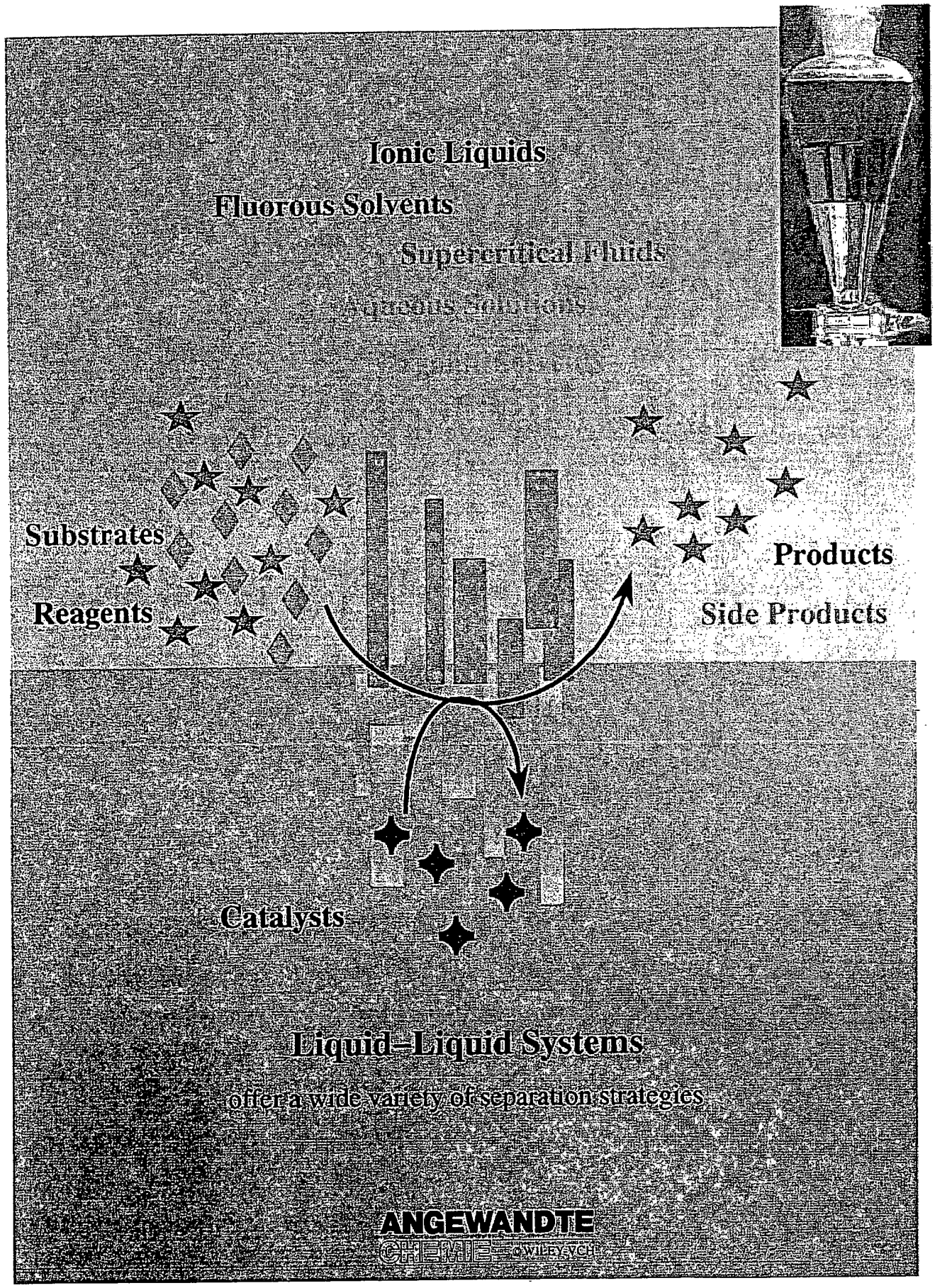
APPENDIX F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Modern Separation Techniques for the Efficient Workup in Organic Synthesis

Carl Christoph Tzschucke, Christian Markert, Willi Bannwarth,* Sebastian Roller, André Hebel, and Rainer Haag*

The shift of paradigm in combinatorial chemistry, from large compound libraries (of mixtures) on a small scale towards defined compound libraries where each compound is prepared in an individual well, has stimulated the search for alternative separation approaches. The key to a rapid and efficient synthesis is not only the parallel arrangement of reactions, but simple work-up procedures so as to circumvent time-consuming and laborious purification steps. During the initial development stages of combinatorial synthesis it was believed that rational synthesis of individual compounds could only be achieved by solid-phase strategies. However, there are a number of problems in solid-phase chemistry: most notably there is the need for a suitable linker unit, the limitation of the reaction conditions to certain solvents and reagents, and the heterogeneous reaction conditions. Further disadvantages are: the moderate loading capacities of the polymeric support and the limited stability of the solid support. In the last few years several new separation techniques have been developed. Depending on the chemical problem or the class of compounds to be prepared, one can choose from a whole array of different approaches. Most of these modern separation approaches rely on solution-phase chemistry, even though some of them use solid-phase resins as tools (for example, as scavengers). Several of these separation techniques are based on liquid–liquid phase separation, including ionic liquids, fluorous phases, and supercritical solvents. Besides being benign with respect to their environmental aspects, they also show a number of advantages with respect to the work-up procedures of organic reactions as well as simplicity in the isolation of products. Another set of separation strategies involves polymeric supports (for example, as scavengers or for cyclative cleavage), either as solid phases or as soluble polymeric supports. In contrast to solid-phase resins, soluble polymeric supports allow reactions to be performed under homogeneous conditions, which can be an important factor in catalysis. At the same time, a whole set of techniques has been developed for the separation of these soluble polymeric supports from small target molecules. Finally, miscellaneous separation techniques, such as phase-switchable tags for precipitation by chemical modification or magnetic beads, can accelerate the separation of compounds in a parallel format.

Keywords: biphasic catalysis · combinatorial chemistry · parallel synthesis · polymeric supports · separation techniques

[*] Prof. Dr. W. Bannwarth, Dipl.-Chem. C. C. Tzschucke, Dipl.-Chem. C. Markert
Institut für Organische Chemie
Albert-Ludwigs-Universität Freiburg
Albertstrasse 21, 79104 Freiburg (Germany)
Fax: (+49) 761-203-8705
E-mail: willi.bannwarth@organik.chemie.uni-freiburg.de
Dr. R. Haag, Dipl.-Chem. S. Roller, Dipl.-Chem. A. Hebel
Freiburger Materialforschungszentrum
und Institut für Makromolekulare Chemie
Albert-Ludwigs-Universität Freiburg
Stefan-Meier-Strasse 21, 79104 Freiburg (Germany)
Fax: (+49) 761-203-4709
E-mail: rainer.haag@fmf.uni-freiburg.de

1. Introduction

Combinatorial synthesis[1, 2] is regarded as one of the key disciplines for providing the constant supply of chemical compounds that may be monitored for their biological activity on the vastly increasing number of biological targets. Together with high-throughput screening formats and efficient data management this will undoubtedly lead to an acceleration in the process of drug discovery. The initial focus in combinatorial chemistry was on the rapid synthesis of highly complex mixtures comprising minute amounts of individual compounds. This strategy became prominent because of the ingenious split-and-combine approach and tagging strategies

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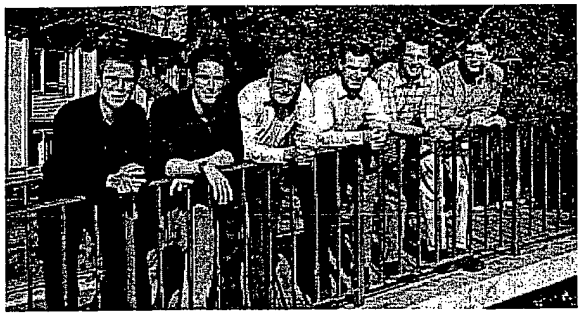
to simplify deconvolution once activity on a biological target had been observed. Although this strategy offers a minimum synthetic effort per prepared compound it has been largely substituted by the preparation of individual compounds in amounts of 1–50 mg by the use of parallel synthesis. One reason for this shift of paradigm was the tedious deconvolution process after screening, which resulted quite often in false positives. The individually pure compounds prepared by parallel synthesis can be characterized and stored in easily accessible repositories which contain sets of highly diverse compounds. As a consequence of the high purity of the compounds the screening data are reliable.

During the initial development stages of combinatorial synthesis—possibly biased by the straightforward solid-phase



From left to right: C. Markert, S. Roller, W. Bannwarth, R. Haag, A. Hebel, C. C. Tzschucke

C. Christoph Tzschucke was born in 1975 in Offenburg and studied chemistry from 1995–2001 at the Universität Freiburg, Germany. In 1997/98 he worked with Prof. H. J. Reich, University of Wisconsin, Madison (USA). Since 2001 he has worked as a PhD student in the group of Prof. W. Bannwarth. His research is centered on perfluoro-tagged ligands and catalysts.

Christian Markert was born in 1975 in Freiburg and studied chemistry at the Universität Freiburg from 1995 until 2001, when he completed his Diploma thesis with Prof. W. Bannwarth. During the academic year 1997/98 he studied at UMIST, Manchester (UK), in the group of Prof. S. Holmes. Since March 2002 he has been a PhD student in the research group of Prof. A. Pfalz, Universität Basel (Switzerland).

Willi Bannwarth was born in 1947 in Bad Säckingen and started his career as a laboratory technician and chemical engineer. Afterwards he studied chemistry at the Universität Münster, where he wrote his Diploma thesis on anionic cycloadditions while working with Prof. T. Kauffmann. After his doctoral studies on the synthesis of pteridine nucleotides with Prof. W. Pfleiderer, Konstanz, he was a postdoctoral fellow with Sir A. Battersby in Cambridge (UK). From 1979 until 1996 he worked at Roche Basel (Switzerland). In 1992 he finished his Habilitation in organic chemistry at the Universität Konstanz. From 1996 until 1999 he worked at Byk Gulden Pharmaceuticals in Konstanz, where he established a "new technologies" section. Since 1999 he has been professor for organic chemistry at the Universität Freiburg. His research interests are bioorganic and combinatorial chemistry.

Sebastian Roller was born 1973 in Würzburg (Germany) and studied chemistry at the Albert-Ludwigs-Universität Freiburg from 1996 until 2002. Since April 2002 he has been working on his PhD thesis at the institute of macromolecular chemistry of the Albert-Ludwigs-Universität Freiburg with Dr. Rainer Haag in the department of Prof. Rolf Mülhaupt. His research interests are the development and application of high-loading polymeric supports in organic synthesis, immobilization of reagents, and catalysts.

André Hebel was born in 1973 in Kamp-Lintfort and studied chemistry between 1994 and 1999. He completed his basic study at the Gerhard-Mercator University in Duisburg (1994–1996) and then moved to the Philipps-Universität Marburg (1996–1999), where he received his Diploma degree in 1999. Since January 2000 he has been working on his PhD thesis at the institute of macromolecular chemistry of the Albert-Ludwigs-Universität Freiburg with Dr. Rainer Haag in the department of Prof. Rolf Mülhaupt. His research interests are dendritic polymers as high-loading soluble supports for reagents and catalysts with application in multiparallel organic synthesis.

Rainer Haag was born in 1968 in Darmstadt and studied chemistry at the TU Darmstadt and the Universität Göttingen (1987–1992). In 1995 he completed his PhD thesis on highly strained acepentalene derivatives with Prof. A. de Meijere. During several research fellowships he worked with Prof. M. Vandewalle, Rijksuniversität Gent, Belgium (1991 as ERASMUS student); with Prof. M. Rabinovitz, Hebrew University, Jerusalem, Israel (1994 as research fellow); with Prof. S. V. Ley, University of Cambridge, England (1996–1997 as a postdoctoral fellow); and with Prof. G. M. Whitesides, Harvard University, Cambridge, USA (1997–1999 as a postdoctoral fellow). Since 1999 he has been assistant professor (Habilitand) at the institute of macromolecular chemistry and materials research center of the Albert-Ludwigs-Universität, Freiburg. His research interests include dendritic polymers as highly functional supports for combinatorial synthesis and drug delivery, as well as self-assembled monolayers for biologically active surfaces. He has been recipient of the ADUC-Habilitanden-Prize 2000 of the GDCh, the Reimund-Stadler-Prize 2001 of the Macromolecular Chemistry division, and the Heinz Maier-Leibnitz-Prize 2002 of the German Research Foundation (DFG).

synthesis of oligonucleotides and peptides—it was believed that rational synthesis of individual compounds could only be achieved by solid-phase strategies. The main advantage of solid-phase synthesis is that larger excesses of reagents may be applied, thereby driving the reactions to completion. Moreover, the excesses of reagents can be removed after the reaction by simple filtration procedures, thus avoiding time-consuming purification steps. Besides the need for two additional steps involved in chemistry on solid supports, namely the attachment of the starting material and the release of the product, there are a number of difficulties involved in solid-phase chemistry. Most notably there is the need for a suitable linker unit, the limitation of the reaction conditions to certain solvents and reagents, the heterogeneous reaction conditions, the moderate loading capacities (typically < 1.5 mmol g^{-1}), the stability of the solid support, the cumbersome monitoring of the reaction, and the identification of the compounds attached to the solid support. A number of alternative solution approaches and the use of solid-phase-bound reagents and scavengers have emerged because of these difficulties.

The key to a rapid and efficient synthesis is not only the parallel arrangement of reactions, but easy to perform work-up procedures that will circumvent time-consuming and laborious purification steps so that they can be carried out in a parallel fashion. There is no general principle for achieving this goal, but during the last few years several new techniques have been developed. Depending on the chemical problem or the class of compounds to be prepared, one can choose from a whole array of different approaches. In this review we have summarized and compared the latest (since ca. 1999) achievements in this area since the previous review by Curran in 1998.[3] We have also focused on separation techniques which are simple enough that the work-up can be performed in a parallel format and might be suitable for process automation.

used to provide biphasic systems for catalysis. In such systems the transition-metal catalyst resides in the second phase (ionic liquid or fluorous phase) whereas the products and starting materials are dissolved in the organic phase. The reactions are carried out under vigorous stirring and/or heating. After the reaction, the layers are reformed and separated by decantation and/or extraction (Figure 1). The catalyst in the ionic liquid or fluorous phase can be reused. The only prerequisite is that the starting materials have to be at least partially soluble in the second phase to guarantee respectable reaction rates. This principle has been demonstrated for a number of catalytic processes. For many applications of reactions in ionic liquids, where the starting material and the product represent liquids themselves, there is no need to add an organic solvent to create the biphasic system. Alternatively, the reaction can be carried out in the ionic liquid and after the reaction it is extracted with an organic solvent to isolate the products. If the products are volatile enough they can be distilled directly from the ionic liquid. In both cases the catalyst remains in the ionic liquid and can be reused. Examples of parallelization and automation in the case of liquid–liquid-phase separation are rare; however, many robotic systems are now able to separate liquid phases which will enhance automation of these techniques in the future.

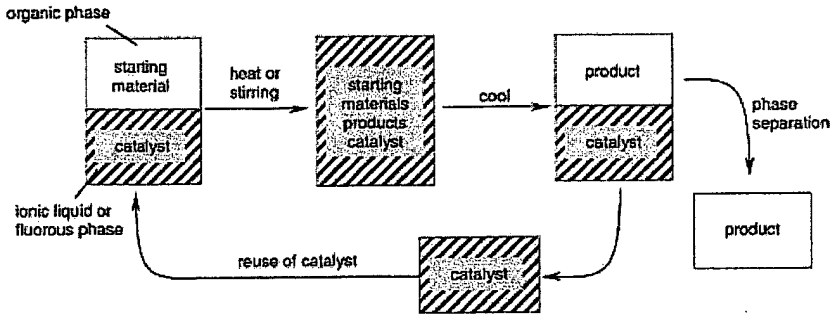


Figure 1. Principle of a simple work-up procedure when using fluorous-phase chemistry or ionic liquids.

2. Liquid–Liquid-Phase Separation

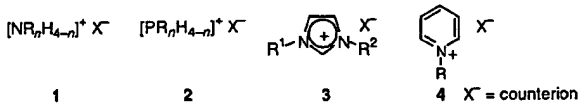
The majority of chemical reactions are carried out in an organic solvent. These solvents can have detrimental effects on the environment and human health as a result of inflammability, volatility, and toxicity. Hence, tremendous efforts have been made during the last decade to replace hazardous organic solvents by alternative reaction media. These encompass water, supercritical media (especially supercritical CO_2), perfluorinated solvents, and ionic liquids. Besides being benign with respect to their environmental aspects, they also show a number of advantages with respect to work-up procedures used in organic reactions as well as simplicity of product isolation.

Ionic liquids and perfluorinated solvents are not miscible with a number of organic solvents. Such combinations can be

2.1. Ionic Liquids

Ionic liquids represent salts with a low melting point ($< 100\,^{\circ}C$). Their vapor pressure is negligible below their decomposition temperatures and, thus, no ionic liquid used as a reaction media is lost by evaporation. Some of the ionic liquids show liquid behavior over a range of several hundred degrees centigrade and thus they can be employed over a wide temperature range.[4–8]

The common classes of ionic liquids comprise: Alkyl ammonium salts (**1**), alkylphosphonium salts (**2**), *N*,*N*′-dialkyl



1 **2** **3** **4** X$^-$ = counterion

imidazolium salts (**3**), and *N*-alkyl pyridinium salts (**4**), of which the *N,N'*-dialkyl imidazolium salts have attracted particular attention since they are easily prepared and are liquid over a wide range of temperatures.

Ionic liquids have been used as solvents for numerous organic and inorganic reactions. The physical and chemical properties vary depending on the combination of cation and anion. Hence, their properties can be modulated and adapted to the chemical reaction for which the ionic liquid is envisaged by varying the anions and cations. Ionic liquids composed of weakly coordinating ions represent highly polar, yet non-coordinating solvents. The solvent properties are largely determined by their ability to act as a hydrogen-bond donor or acceptor and the degree of delocalization of the anionic charge. Their ability to form hydrogen bridges also has an influence on the viscosity of the ionic liquids. A low tendency to form hydrogen bridges occurs in parallel with low viscosity. Variation of the chain length of the alkyl substituents on the cation or anion allows the lipophilicity to be adjusted. Increased chain lengths lead to higher lipophilicity.

A number of ionic liquids are air and moisture stable and are relatively easy to handle. Some of them, for example, most of the imidazolium and ammonium salts, are hygroscopic and reactions involving these ionic liquids are best carried out under an inert atmosphere. The nature of the pertinent anion not only has an affect on the melting behavior (Table 1) and the handling properties, it also affects the stability as well as the acidity of the ionic liquid.

Table 1. Effect of the anion on the melting point of $[EMIM]^+X^-$.[a]

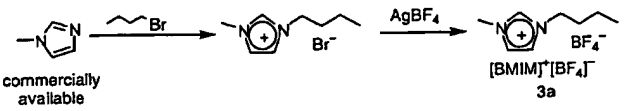
$[X]^-$	M.p. [°C]
Cl^-	87
NO_3^-	55
$AlCl_4^-$	7
BF_4^-	6
$CF_3SO_3^-$	−9

[a] EMIM = 1-ethyl-3-methylimidazolium.

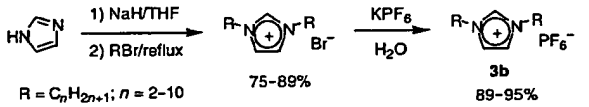
Salts with NO_3^-, $PhSO_3^-$, and $N(SO_2CF_3)_2^-$ counterions are air and moisture stable, while $AlCl_4^-$ salts are hygroscopic and moisture sensitive. Salts with $Al_2Cl_7^-$ counterions show acidic behavior which can have a beneficial effect on activation the catalysts used in ionic liquids. Recently, it was reported that the combination of dicyanamide (dca) anions with cations of the type **1**, **3**, and **4** gave ionic liquids with low viscosity and water miscibility. Furthermore, these ionic liquids show donor characteristics as a consequence of the ligand properties of the anion.[9]

2.1.1. Synthesis of Ionic Liquids

Ionic liquids are prepared starting from the corresponding amine or phosphane in a two-step procedure. Alkylation leads to quarternization of the nitrogen or the phosphorus atom, respectively. This process is usually followed by anion metathesis with an alkali or ammonium salt of the desired anion. This principle is illustrated in Scheme 1 for the preparation of $[BMIM]^+[BF_4]^-$ (**3a**, BMIM = 1-*n*-butyl-3-methylimidazolium).[10, 11] Alternatively, the anion exchange can be achieved by using an ion-exchange resin. If after the alkylation step the anion is a halogenide, it can also react with a Lewis acid to create the desired anion (for example, $AlCl_4^-$). It has been postulated for a long time that the unsymmetrical nature of the cation plays a major role in the low melting point of imidazolium-derived ionic liquids. Recently it was demonstrated that symmetrical imidazolium salts such as **3b** are also room-temperature ionic liquids (Scheme 2).[12]



Scheme 1. Preparation of $[BMIM]^+[BF_4]^-$ (**3a**).



Scheme 2. Synthesis of the C_2-symmetrical ionic liquid **3b**.

High purity of ionic liquids is of prime importance for achieving reliable synthesis in these media. Therefore, all the steps involved in their preparation have to proceed with high efficiency, since purification after synthesis is extremely tedious. Some of the ionic liquids, especially the ones with imidazolium as the cation, are commercially available. Their price is still very high, which to a certain extent prevents their application for routine synthesis.

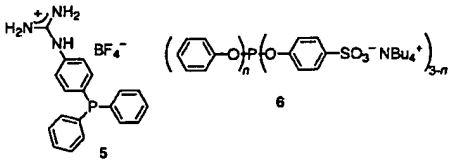
2.1.2. Work-Up and Isolation Procedures

The beneficial effects of ionic liquids in regard to environmental aspects that result from their nonvolatility has already been alluded to in Section 2.1. In addition to that, ionic liquids allow for simple work-up procedures and straightforward isolation protocols for products, particularly with respect to transition-metal catalysis.

Ionic liquids with noncoordinating anions represent highly polar organic solvents that dissolve polar transition-metal complexes without usually affecting their properties. In general, they allow immobilization of the complex in the ion liquid without modification of the ligands. In a number of cases, ionic liquids have a beneficial effect on the catalytic reaction, which proceeds more efficiently than in organic solvents. Under these circumstances the ionic liquid acts not only as a solvent but also as a co-catalyst. The reason for this may be a better stabilization of the transition state or activation of the catalyst (as a result of the Lewis acidity of the ionic liquid)[13] or the formation of carbene-like ligand structures.[14]

In applications where the starting material and the product represent liquids themselves, there is no need to add an organic solvent to create the biphasic system. This was demonstrated for the hydrogenation of olefins.[10, 15] Alternatively, the reaction can be carried out in the ionic liquid and

the product is isolated by extraction with an organic solvent. The products can be distilled directly from the ionic liquid if they are sufficiently volatile. In both cases the catalyst remains in the ionic liquid and can be reused. In some examples a small leaching of the catalyst out of the ionic liquid into the organic layer was observed. This effect can be minimized by modification of the ligands with ionic groups as shown in the P^{III} ligands **5**–**7**.[16]



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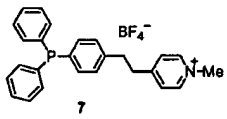

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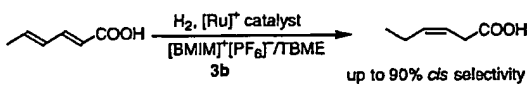
Ionic liquids as reaction media allow for parallel arrangements of reactions followed by straightforward isolation of the products and hence for the rapid synthesis of compounds. So far, this potential has not yet been exploited. This is because of the still limited number of types of reactions which have been carried out in ionic liquids and because of the relatively high costs involved.

2.1.3. Homogeneous Catalytic Reactions in Ionic Liquids

2.1.3.1. Hydrogenations

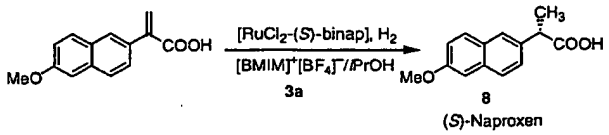
There are a number of catalysts available for homogeneous hydrogenations. In the first reported examples of homogeneous hydrogenations involving ionic liquids the starting material and the product represented highly lipophilic liquids (for example, hydrogenation of hexene or cyclohexene) in which the polar catalyst was immobilized without any modification in the ionic liquid and no additional organic solvents were necessary for the isolation of the product. The solubility of hydrogen in ionic liquids seems to be high enough to obtain respectable reaction rates.[10, 15]

Recently, an interesting example of stereoselective hydrogenation in a biphasic system consisting of $[BMIM]^+[PF_6]^-$/TBME was reported to give high selectivity for *cis*-3-hexanoic acid (Scheme 3).[17]



Scheme 3. Stereoselective hydrogenation in **3b**/TBME to give *cis*-3-hexanoic acid.

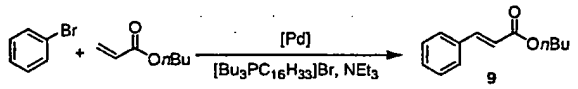
Enantioselective hydrogenation in biphasic systems formed by ionic liquids and organic solvents is also possible. This was first demonstrated for the hydrogenation of acetamidocinnamic acid in a mixture of $[BMIM]^+[BF_4]^-$/isopropanol to give (*S*)-phenylalanine (64% *ee*).[15] The same biphasic system was applied to the hydrogenation of aryl acrylic acids with a [Ru-binap] catalyst as illustrated in the preparation of (*S*)-naproxen (**8**, Scheme 4).[18] The catalyst was reused after phase separation and isolation of the product.



Scheme 4. Preparation of (*S*)-naproxen by hydrogenation in **3a**/*i*PrOH.

2.1.3.2. Carbon–Carbon Coupling Reactions

Pd-catalyzed carbon–carbon bond forming reactions have received considerable attention as a consequence of their enormous synthetic potential. The Heck reaction in particular has found widespread application for the synthesis of olefins by Pd-mediated vinylation of aryl halides. The reaction is best performed in polar organic solvents such as DMF or NMP. A relatively large amount of catalyst (> 1 mol%) is required for satisfactory conversions and recycling of the catalyst is hampered by decomposition. It was reported that these shortcomings could be overcome by use of an ionic liquid. The first example involved the coupling of bromobenzene with *n*-butyl acrylate to yield *trans*-cinnamic *n*-butyl ester **9** in tetraalkyl ammonium- and tetraalkyl phosphonium derived ionic liquids of type **2** (Scheme 5).[19] The ionic liquid was reported to have a stabilizing effect on the Pd catalyst such that it could be reused for several consecutive runs.



Scheme 5. Heck reaction leading to *trans*-cinnamic *n*-butyl ester.

The same reaction was also carried out in $[BMIM]^+[PF_6]^-$ as the solvent and $Pd(OAc)_2$ or $PdCl_2$ as the catalyst with NEt_3 as the base. The products were isolated by extraction with hexane and the catalyst could be reused several times.[20] It was also demonstrated that Pd/C and NEt_3 could also be used successfully as the reusable catalyst and base, respectively.[21] Böhm and Herrmann have investigated the Heck reaction in ionic liquids in great detail and have shown impressively the advantages of ionic liquids over conventional solvents. A striking feature is the stabilization and the activation of the Pd catalyst: even $Pd(OAc)_2$ or $Pd(PPh_3)_4$ can be used in the absence of additional phosphanes to couple chloroarenes. The products were either extracted or distilled from the ionic liquid and the catalyst was used for several consecutive runs.[22]

Xiao and co-workers found that Heck reactions carried out in $[BMIM]^+Br^-$ proceeded more efficiently and gave a higher selectivity for the *trans* product than those carried out in $[BMIM]^+[BF_4]^-$.[14] The in situ formation of heterocyclic carbene complexes by deprotonation of BMIM-derived ionic liquids was proposed to explain this finding (Figure 2a). Calò et al. used Pd–benzothiazole carbene complexes directly for Heck reactions in tetrabutylammonium bromide (TBAB;

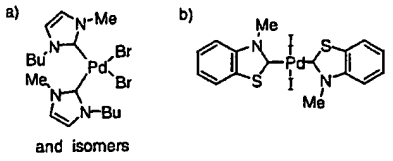
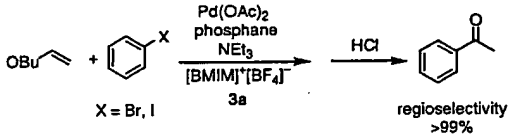


Figure 2. Pd–carbene complexes formed in situ in ionic liquids.

Figure 2b. They demonstrated that very fast and efficient couplings occurred, especially for the preparation of β,β-diaryl acrylates. Recycling of the catalyst was impaired and only three consecutive runs could be performed.[23, 24]

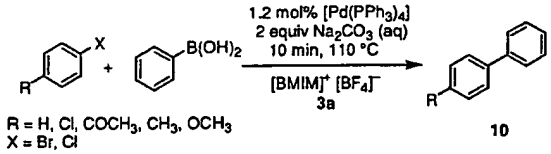
The Heck arylation of electron-rich olefins such as enol ethers leads to a mixture of regioisomers. Regioselective substitution at the olefinic carbon atom α to the oxygen atom can only be achieved when aryl halides are replaced by the corresponding triflates or when a stoichiometric amount of silver triflate or thallium acetate is added. Aryl halides can be transformed in $[BMIM]^+[BF_4^-]$ and the reaction proceeds with high efficiency and high regioselectivity (Scheme 6). The ionic



Scheme 6. Heck reaction for the regioselective formation of acetophenone.

liquid not only promotes the ionic pathway of the Heck reaction to give the α-arylated product but leads at the same time to an acceleration of the reaction.[25] Recently, it was demonstrated that under ultrasonic irradiation the Heck reaction in ionic liquids proceeds at ambient temperature (30 °C) with reaction times of 1.5–3 h.[26] The products were separated from the catalyst by extraction with 10% ethyl acetate in petroleum ether and purified by chromatography. The catalyst could be reused at least three times.

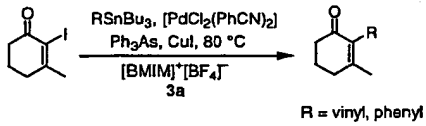
The first example of Suzuki cross-coupling reactions in $[BMIM]^+[BF_4]^-$ was reported recently (Scheme 7).[27] Compared to standard protocols for Suzuki couplings, a significantly increased activity of the applied $[Pd(PPh_3)_4]$ complex



Scheme 7. Suzuki coupling in 3a.

was observed during the formation of the desired biphenyl derivatives **10**. Only minimal formation of the homocoupling product could be detected, which simplified the work-up. The desired products were obtained by extraction with diethyl ether, by sublimation, or precipitation after the addition of water, with no leaching of the catalyst into the product. The catalyst was recycled at least three times without loss of activity. Suzuki coupling reactions in ionic liquids could also be promoted by ultrasound irradiation to proceed at ambient temperature.[28]

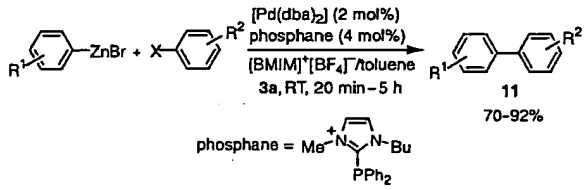
Stille couplings were also reported (Scheme 8).[29] The products were isolated by extraction with diethyl ether and the $[BMIM]^+[BF_4]^-$ catalyst could be recycled five times with no (for Pd^{II} systems) or only a slight loss in activity (for Pd^0 systems). In addition, the ionic-liquid layer was stored for



Scheme 8. Stille coupling in 3a.

several weeks after extraction with no special precautions to exclude air or moisture, and gave the same coupling yields as a freshly prepared catalyst solution.

The Negishi coupling of organozinc compounds and aryl iodides was demonstrated in a two-phase system composed of $[BMIM]^+[BF_4]^-$ and toluene (Scheme 9).[30] In most cases the reaction proceeded within a few minutes at room temperature and led to the desired cross-coupling products **11**. Aryl bromides and aryl nonaflates required longer reaction times. After the reactions the ionic liquid containing the catalyst was separated from the toluene by decantation and was reused for subsequent coupling reactions. After the third cycle a significant decrease in the yield was observed.



Scheme 9. Negishi coupling in 3a.

The homocoupling of aryl halides in $[BMIM]^+[PF_6]^-$ with $[(PPh_3)_nNi^0]$ as the catalyst was reported recently.[31] The desired biaryls were obtained in moderate to good yields after extraction with diethyl ether. The catalyst was recycled but in the second run a decrease in activity was already observed.

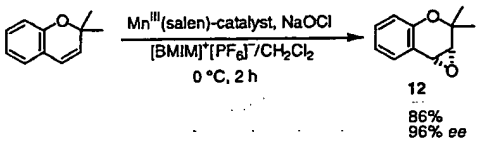
The Pd^0-catalyzed formation of C–C bonds by allylic nucleophilic substitution with C nucleophiles (Tsuji–Trost coupling) was also performed in ionic liquids. In the reaction of malonic acid derivatives with 3-acetoxy-1,3-diphenylprop-1-ene, the anion was formed with K_2CO_3 or DBU directly in $[BMIM]^+[BF_4]^-$ and the coupling products were obtained in high yields.[32] The recycling of the catalyst was only possible after replacement of PPh_3 by the more polar phosphane $P(m\text{-}C_6H_4SO_3Na)_3$ and reactions could be performed three times. The Tsuji–Trost coupling of ethyl cinnamyl carbonate and ethyl acetoacetate was carried out in a biphasic system of $[BMIM]^+Cl^-$/methyl cyclohexane.[33] The reaction proceeded

more efficiently than in water/organic biphasic mixtures and the coupling product was isolated in a yield of 90%. The recycling was hampered by the high solubility of the product in the ionic liquid.

In summary, it can be stated that ionic liquids are ideal media to perform Pd-mediated C–C couplings. In most cases the catalyst can be fixed in the ionic liquid without modification of the ligands. The work-up is easily performed and the products can be separated from the catalyst in the ionic liquid by using lipophilic solvents such as diethyl ether. Both the catalyst and the ionic liquid can be recycled. Ionic liquids can stabilize the Pd catalyst and cause activation, and even unreactive aryl halides can be used. They also allow for the application of "cheap" Pd compounds, such as $PdCl_2$, and the expensive Cs_2CO_3 can often be replaced by less expensive bases.

2.1.3.3. Oxidations

Although a number of ionic liquids are fairly stable towards oxidation, there have been only a very limited number of reports on oxidations in biphasic systems involving ionic liquids. One example is the stereoselective epoxidation using Jacobsen's chiral [Mn^{III}(salen)] complex in a mixture of [BMIM]$^+$[PF_6]$^-$ and CH_2Cl_2 in a ratio of 1:4 (Scheme 10).[34] A considerable activation of the catalyst by the ionic liquid was

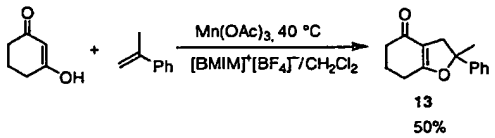


Scheme 10. Stereoselective epoxidation by using the chiral Jacobsen [Mn^{III}salen] complex.

reported. The catalyst was recycled five times and a only small decrease in yield and in *ee* values of **12** was observed. Another epoxidation of alkenes and allyl alcohols in [EMIM]$^+$[BF_4]$^-$ using methyl trioxorhenium (MTO) and urea/H_2O_2 was reported recently.[35] Excellent conversions and selectivities were obtained for a number of substrates. The reaction was performed in a homogeneous fashion since MTO as well as urea/H_2O_2 are completely soluble in [EMIM]$^+$[BF_4]$^-$. The oxidation solution was anhydrous, and opening of the epoxides to form the diols did not occur. Since MTO as well as the ionic liquid are not soluble in diethyl ether, the remaining reactants and products were isolated by extraction with diethyl ether after the reaction.

Oxidations of aromatic aldehydes to the corresponding carboxylic acids were carried out in [BMIM]$^+$[PF_6]$^-$ with oxygen at atmospheric pressure and [Ni(acac)$_2$] (acac = acetyl acetonate) as the catalyst.[36] The yields were lower than the ones obtained for the same type of oxidations carried out in perfluorinated solvents with perfluoroalkyl-tagged acac ligands of Ni^{2+} complexes.[37] The ionic liquid [BMIM]$^+$[BF_4]$^-$ was used in the oxidation of codeine methyl ether to thebaine with MnO_2.[38] The yield was rather low when the oxidation was carried out directly in the ionic liquid with sonication. Performing the oxidation in THF under sonication followed by selective extraction of MnO_2 and other inorganic by-products enabled thebaine to be isolated in high yield.

Carbonyl compounds such as β-diketones or β-ketoesters can be oxidized with $Mn(OAc)_3$ to form radicals which can then undergo carbon–carbon bond-forming reactions. The reaction has to be carried out under harsh conditions which limits its scope of application severely. It was demonstrated that performing the reactions in [BMIM]$^+$[BF_4]$^-$/CH_2Cl_2 yielded the desired products **13** in respectable yields (Scheme 11).[39] At the end of the reaction the $Mn(OAc)_2$ was recovered by precipitation and after filtration it was re-



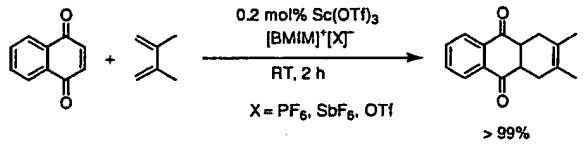
Scheme 11. $Mn(OAc)_3$ oxidations leading to C–C bond formations.

oxidized by $KMnO_4$ and reused. The ionic liquid was also recycled without detriment to the product yields.

2.1.3.4. Diels–Alder Reactions

Several authors have investigated Diels–Alder reactions in ionic liquids. The first reported example was the cycloaddition of cyclopentadiene with crotonaldehyde or methacrolein as dienophiles in dialkyl imidazolium salts as ionic liquids.[40] The results clearly demonstrated that the ionic liquid acted as a Lewis acid which allowed the reaction to be performed at low temperature and which led to a high *endo*:*exo* selectivity. These results were confirmed later for the same type of diene and dienophiles.[41–43] A recycling of the ionic liquid was demonstrated as well.

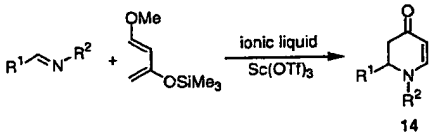
An impressive study on Diels–Alder reactions was reported recently in which a number of different dienophiles were treated with a selection of dienes in [BMIM]$^+$[X]$^-$ in the presence of 0.2 mol% $Sc(OTf)_3$ (an example is shown in Scheme 12).[13] The reaction proceeded with high yields with



Scheme 12. Diels–Alder reaction in an ionic liquid catalyzed by $Sc(OTf)_3$.

PF_6^-, SbF_6^-, and OTf^- counterions. The type of anion had only little effect on the catalytic activity. The *endo*:*exo* selectivity was generally higher than for the same reaction in CH_2Cl_2. After completion of the reaction and extraction of the product with diethyl ether, the ionic liquid phase containing the $Sc(OTf)_3$ was recovered. The ionic-liquid phase was reused 11 times without any loss of activity.

Recently, aza-Diels–Alder reactions for the preparation of 6-aryl-5,6-dihydro-4-pyridones (**14**) in ionic liquids were reported (Scheme 13).[44] The imine dienophiles were prepared in situ from the aldehyde and the amine directly in the ionic liquid. The ionic liquid used was 8-ethyl-1,8-diazabicyclo[5.4.0]-7-undecenium trifluoromethanesulfonates. The yield could be increased significantly by the addition of $Sc(OTf)_3$ in a microencapsulated form. The products were isolated by extraction with diethyl ether and the ionic liquid together with the microencapsulated Lewis acid were reused. The same high yields as observed in the first run were obtained.

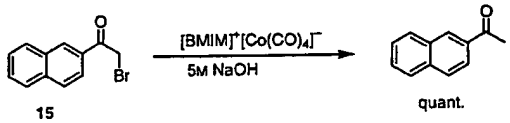


Scheme 13. Aza-Diels–Alder reaction in ionic liquids.

2.1.3.5. *Miscellaneous Reactions*

In the last few years an increasing number of reports have appeared on synthetic methods which take advantage of the favorable properties of ionic liquids. Among the reported reactions are hydroformylations in $[BMIM]^+$-derived ionic liquids in which the aldehydes are formed in remarkably high *n/iso* ratios,[45] [Cr(salen)]-catalyzed ring-opening reactions of epoxides with $TMSN_3$,[46] electrophilic nitrations of aromatic compounds,[47] the Biginelli multicomponent reaction for the preparation of 3,4-dihydropyrimidin-2-(1*H*)-ones,[48] and nucleophilic displacement reactions.[49]

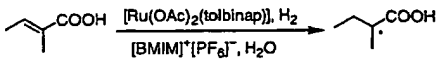
It was outlined in Section 2.1 that the anion of the ionic liquid may also be catalytically active, as observed for example with chloroaluminate anions which can act as Lewis acids. An interesting example in this respect is the application of $[BMIM]^+[Co(CO)_4]^-$ as both solvent and reagent for the debromination of 2-bromoketones **15** (Scheme 14).[50]



Scheme 14. Debromination of 2-bromoketones in/with $[BMIM]^+[Co(CO)_4]^-$.

2.1.3.6. *Combination of Ionic Liquids and Supercritical CO_2*

Recently, the combination of an ionic liquid and supercritical carbon dioxide ($scCO_2$) has emerged as a new system for biphasic homogeneous catalysis. Supercritical CO_2 is soluble in ionic liquids and decreases their viscosity, thereby enhancing the mass transfer. On the other hand, ionic liquids are not particularly soluble in $scCO_2$. Hence, nonvolatile compounds can be extracted quantitatively out of ionic liquids by $scCO_2$ without any contamination. This was first demonstrated by the extraction of naphthalene from $[BMIM]^+[PF_6]^-$ by $scCO_2$.[51] Recently, the system was applied to batch-wise asymmetric hydrogenation (Scheme 15). The product was extracted out of the ionic liquid by $scCO_2$ after the reaction and the catalyst could be reused for four further runs.[52, 53]



Scheme 15. Asymmetric hydrogenation in an ionic liquid followed by extraction with $scCO_2$.

Another example was reported for the batch-wise hydrogenation of CO_2 and alkenes using Wilkinson's catalyst.[54] Hydroformylation reactions[55] and the Ni-catalyzed hydrovinylation of styrene were reported.[56] More recently, the ionic liquid/$scCO_2$ system was extended to continuous flow processes.[57, 58]

2.2. Perfluorinated Systems

Since the seminal work by Vogt[59] and by Horváth and Rábai[60] perfluorinated solvents and compounds with fluorous labels have emerged as powerful tools in synthetic organic chemistry. Not surprisingly, fluorous systems (Fluorous Biphasic System, FBS) have been the subject of several recent reviews.[61–66]

Perfluoroalkanes and—to a certain degree—perfluorinated ethers and amines show a very low miscibility with common organic solvents. The miscibility is temperature dependent and increases with increasing temperature.[67] This phase behavior can be employed to separate molecules with complementary solubilities in organic and fluorous solvents.[68] Perfluorinated solvents are exceedingly hydrophobic and chemically inert. They are considered to be of low toxicity and they are thought to have no ozone-depletion potential, although they do exhibit long atmospheric lifetimes (> 2000 years), which makes them potent greenhouse gases. This situation should be taken into account when using or disposing of perfluorinated solvents.[69]

According to the alchemists rule "similia similibus solvuntur" the solubility of a compound in perfluorinated solvents can be enhanced by attaching long perfluoroalkyl chains (perfluoro tags) to the molecule. The assumption that a fluorine content exceeding 60% (of the molecular weight) is needed to gain differential solubility in fluorous solvents has been reiterated in the literature. This value cannot be more than a rough approximation, since solubilities and partitioning coefficients are dependent on a number of structural features.[70–72] In general, the preferential relative solubility in the fluorous solvent is augmented as the length and number of perfluoroalkyl chains attached to it increase and the polarity of the molecule decreases. However, the absolute solubility of the compound drops as

the length of the perfluoroalkyl chains increases. On the other hand common organic compounds, even very unpolar ones such as *n*-alkanes, show very low partitioning into the fluorous phase.

As mentioned above, the immiscibility of fluorous and organic solvents in conjunction with the differential solubilities can be used to separate molecules with a fluorous label from unlabeled compounds. This possibility leads to a multitude of different separation and purification strategies. The common denominator is that one specific component with a fluorous label (for example, catalyst, reagent, by-product, product) is preferentially soluble in the fluorous phase, while the other components of the reaction mixture (product, starting material, reagents, impurities) are soluble in the organic layer. Depending on the application and the partitioning coefficients, the separation can be performed as a conventional liquid–liquid extraction, as a continuous extraction, or as a solid-phase extraction with fluorous reversed-phase silica gel (FRPSG).[73]

In principle, fluorous techniques are similar to other phase-labeling strategies, such as those based on water-soluble reagents or catalysts and solid-phase-bound reagents, catalysts, or substrates. The logic governing such separation strategies has been reviewed.[3]

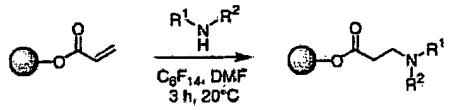
2.2.1. *Perfluorinated Solvents as Reaction Media*

Perfluorinated solvents have found only limited use as reaction media because of their low solvating power. However, this very low miscibility with organic compounds means that products are readily isolated by simple decantation. A perfluorinated solvent can be used to azeotropically remove reaction products and thus shift the equilibrium of the reaction. This principle was demonstrated by Zhu for esterifications and transesterifications as well as for acetal and enamine formation by using a modified Dean–Stark apparatus.[74]

Another interesting feature is the high solubility of gases in perfluorinated solvents;[75] since large amounts of oxygen are soluble they have also been tested as blood substitutes.[76–79] For the same reason they receive attention as reaction media for oxidations. Klement and Knochel have described the oxidation of alkyl zinc compounds to hydroperoxides with molecular oxygen in perfluorohexanes, while mixtures of hydroperoxides and the corresponding alcohols are obtained by the direct oxidation of organometallic compounds in common solvents.[80] Trialkyl boranes have been oxidized to alcohols in a similar manner.[81]

A fluorous biphasic system has been used to spatially separate catalysts in a cascade of ring-closing metathesis (RCM) and a Heck reaction.[82] The RCM was performed at room temperature with the Grubbs catalyst. Since the Grubbs catalysis is not compatible with either palladium acetate nor phosphane ligands, a perfluoro-tagged triphenylphosphane was used. At room temperature the solvent system is biphasic, and the RCM proceeds in the organic phase with the palladium complex residing in the fluorous phase. The mixture becomes homogeneous upon heating and the Heck reaction is catalyzed by the palladium complex. Results obtained with the fluorous phosphane were better than those with a nontagged phosphane, but were not as good as with solid-phase-bound phosphane.

An interesting concept in solid-phase organic synthesis is the use of perfluorinated solvents to accelerate reactions with substrates bound to a polystyrene resin. As a consequence of the low solvating power of the fluorous solvent, the reagent is confined to the resin, thus increasing the local concentration. A small amount of polar cosolvent is needed, possibly to swell the resin (Scheme 16).[83]



Scheme 16. Increase of the local substrate concentration within the resin by a perfluorinated solvent.

2.2.2. *Perfluoro-Tagged Catalysts*

The main field of application for fluorous separation strategies is in fluorous biphasic catalysis (FBC). The catalyst is modified with a fluorous tag, and thus can be removed from the product by extraction with a fluorous solvent. At the beginning of the reaction the perfluoro-tagged catalyst together with the substrate and reagents is present in a biphasic mixture of fluorous and organic solvent. The reaction can proceed either in a heterogeneous fashion with the catalyst in the fluorous phase and the other reactants in the organic phase, or under homogeneous conditions if the reaction temperature is high enough for the biphasic mixture to become monophasic.[84] Upon completion of the reaction, the mixture is cooled to restore the biphasic system. Ideally, the catalyst now remains exclusively in the fluorous layer, while all the product is dissolved in the organic phase. The phases are separated to yield products free of catalyst contaminations, and the fluorous layer containing the catalyst, which can be reused for further reactions.

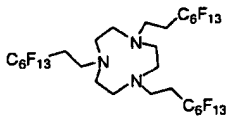
The importance of such catalyst systems lies mainly in the field of combinatorial synthesis and industrial processes. FBC represents a way to simplify work-up and purification in parallel synthesis to give easy extraction procedures, which even allow for automation. This possibility avoids difficult purification procedures such as chromatography or distillation, which would hamper parallel work-up. Thus, compound libraries can be prepared for high-throughput screening. Products without heavy-metal contaminations, which could impair biological assays, are especially important for such applications. In addition to simplified purification, the option of catalyst recycling plays an important role in industrial processes. Expensive catalysts contribute significantly to the cost of a product. Recycling of such a catalyst as well as a simplified product isolation can greatly reduce the costs of a process. To date, a growing number of catalysts has been modified with perfluoro tags (see for example, structures **16**–**20**).

16: [HRh(CO)L$_3$] L = $P(CH_2CH_2C_6F_{13})_3$

17: [PdL$_2$Cl$_2$] L = $P(C_6H_4R^F)_3$ or $P(C_6H_4Si(R^F)_n(CH_3)_{3-n})_3$

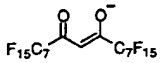
17a: R^F = 4-$CH_2CH_2C_8F_{17}$
17b: R^F = 4-C_8F_{17}
17c: R^F = 3-$CH_2CH_2C_8F_{17}$
17d: R^F = 3-C_8F_{17}
17e: R^F = 4-$OCH_2C_7F_{15}$

R^F = $CH_2CH_2C_6F_{13}$, $CH_2CH_2C_8F_{17}$



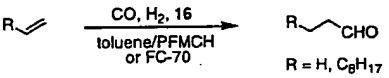
18

19a: [NiL$_2$]
19b: [PdL$_2$]
19c: K[RuL$_3$]

L = 

20: [LaL$_3$] L = $(C_8F_{17}O_2S)_2N^-$ $SO_2C_8F_{17}$

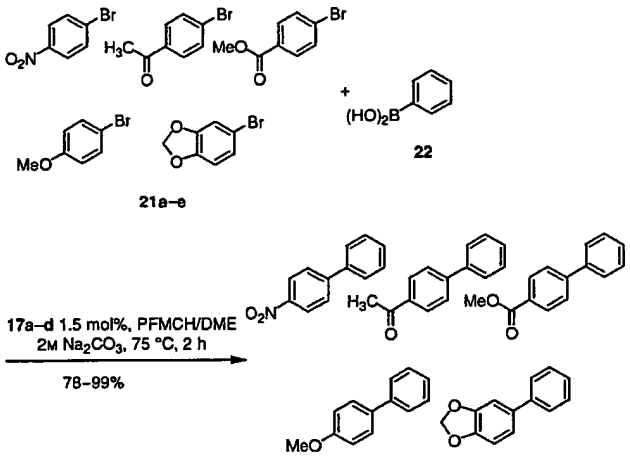
The hydroformylation of terminal olefins was among the first reactions to be performed in FBC.[60, 85] The hydroformylation of 1-decene catalyzed by rhodium complex **16** was studied in detail (Scheme 17). A total turnover number



Scheme 17. Hydroformylation with an in situ generated fluorous rhodium catalyst.

exceeding 35000 with a loss of only 1.18 ppm rhodium per mole of undecanal was achieved in nine consecutive runs using the same fluorous phase containing the catalyst. In the continuous hydroformylation of ethene the resulting propanal was distilled from the high-boiling fluorous phase. No loss of catalyst activity was detected over 60 days. Similar rhodium catalysts have been used for hydrogenations,[86] hydroborations,[87, 88] and hydrosilylations of olefins[89, 90] in fluorous biphasic systems.

Hydrogenation of olefins was also achieved with dendrimer-encapsulated palladium nanoparticles that were soluble in fluorous phases.[91] A bimetallic rhodium catalyst was used in the cyclopropanation of alkenes and recovered by fluorous extraction.[92] The palladium-catalyzed C–C bond-forming reactions that have been performed in fluorous biphasic systems include the Heck reaction,[93] benzannulation of conjugated enynes,[94] palladium-catalyzed allylic substitution[95, 96] as well as Negishi,[97] Stille,[98] Suzuki,[99] and Sonogashira reactions.[100] The Suzuki coupling of five different aryl bromides **21** with phenylboronic acid (**22**) was carried out with four different palladium complexes (**17a–d**, Scheme 18).[99] The fluorous phase was extracted with DME and water and the catalysts reused five times without any loss of activity. The yields of the biaryls were generally high and independent of the phosphane employed.



Scheme 18. Suzuki coupling in PFMCH/DME.

Numerous oxidation reactions have been carried out under fluorous biphasic conditions because of the good solubility of oxygen in perfluorinated solvents. Alcohols were oxidized to aldehydes or ketones with molecular oxygen by using a catalyst system of CuBr, perfluoroalkyl-tagged bipyridine, and 2,2,6,6-tetramethylpiperidine-*N*-oxide (TEMPO). Yields were high for benzylic alcohols, and in one example the catalyst was recovered and reused eight times without any significant decrease in yield.[101] A variety of alcohols was oxidized to aldehydes or ketones with palladium(II) acetate and perfluoro-tagged pyridines as ligands.[102] Although only a small amount of leaching of palladium was observed, the catalytic activity in consecutive runs could be retained only if a small amount of additional ligand was added before every other run.[103]

A series of fluorous β-diketonates **19** of transition metals were prepared.[104] Nickel complex **19a** was used in the aerobic oxidation of aldehydes to carboxylic acids[37] as well as in combination with *i*PrCHO and oxygen for the oxidation of sulfides to sulfoxides or sulfones.[37] This oxidation could also be catalyzed by cobalt complexes with perfluoro-tagged porphyrin or phtalocyanin ligands, but recycling of the catalyst was unsuccessful.[105] Palladium complex **19b** was used as the catalyst for the oxidation of terminal olefins to methyl ketones with *tert*-butylhydroperoxide (TBHP) as oxidant.[106] Oxidation of cyclohexene to cycohexenol and cyclohexenone was achieved with a manganese complex with ligand **18** using oxygen and substoichiometric amounts of TBHP as the oxidant.[107, 108]

Selective epoxidation reactions of internal olefins in the presence of terminal double bonds was achieved by the use of ruthenium complex **19c** and excess *i*PrCHO/oxygen.[37] The epoxidation of olefins has also been catalyzed by perfluoro-tagged cobalt–porphyrin complexes.[109] Asymmetric epoxidations were achieved with perfluoro-tagged

manganese–salen complexes.[110–112] A fluorous aryl selenic acid catalyst for the epoxidation of olefins with hydrogen peroxide could be recycled ten times without loss of catalytic activity.[113]

Friedel–Crafts acylations and other Lewis acid promoted reactions were carried out in FBS using fluorous lanthanide methides **20**. High yields were reported, and the Lewis acid was quantitatively recovered by phase separation and reused in several consecutive runs.[114, 115]

Fluorous tin oxides have been used in transesterifications[116] and in the monotosylation of 1,2-diols.[117] The enantioselective addition of diethylzinc to aldehydes has been performed with different perfluoro-tagged catalysts.[118–121]

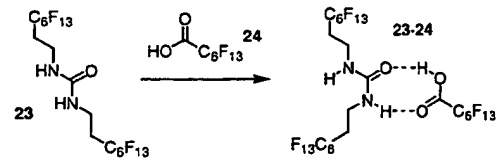
Recently, Gladysz and co-workers employed the fluorous phosphane $P(CH_2CH_2C_8F_{17})_3$ as catalyst for the addition of alcohols to the triple bond of methyl propiolate:[122] During the reaction, the phosphane was dissolved in octane at 65 °C. Subsequently, the catalyst was precipitated at −30 °C and separated by decantation. No fluorous solvent was needed.

2.2.3. *Perfluoro-Tagged Reagents*

After any reaction, chemists are faced with the problem of isolating the product. This is done by exploiting more- or less-pronounced differences in the physical properties of product and impurities. Simple purification procedures are needed in combinatorial syntheses of libraries for high-throughput screening.[123] Furthermore, the procedure should be the same for every compound of a library to allow for automation and parallel synthesis. Similar to the situation of catalysis described in Section 2.2.2, perfluoro-tagged reagents can be used to easily separate reaction by-products and excess reagents from the product. This is achieved either by extraction with a fluorous solvent or by filtration over FRPSG. The resulting solution should now contain only organic molecules while the fluorous phase retains the perfluoro-labeled reagent. Therefore, a large excess of reagent can be used to ensure complete conversion.[124] This approach is especially attractive if reagents or by-products are toxic, expensive, or difficult to remove. The strategy is similar to the use of solid-phase-bound reagents, but since the fluorous reagents are individual soluble molecules their behavior is closer to conventional soluble compounds, and under appropriate conditions the reaction can proceed homogeneously.

The use of trialkyl tin reagents and selenium compounds has been limited by their toxicity. Fluorous tin reagents have been used in radical dehalogenations,[125] in the allylation of aldehydes,[126, 127] and in Stille coupling reactions.[128] Fluorous tin azide was used in the synthesis of tetrazoles.[124] Perfluoro-tagged aryl selenium reagents were employed in the conversion of carbonyl compounds to their α,β-unsaturated derivatives and in the reduction of dimesylates to alkenes.[129, 130]

The partitioning coefficient of bis(perfluoroalkyl)ureas **23** between perfluorohexane and CH_2Cl_2 could be significantly increased by the addition of perfluoroalkanoic acids **24** (Scheme 19). This is thought to be the result of hydrogen bonding between the urea and the acid, which results in complex **23**·**24** which is less polar than the individual

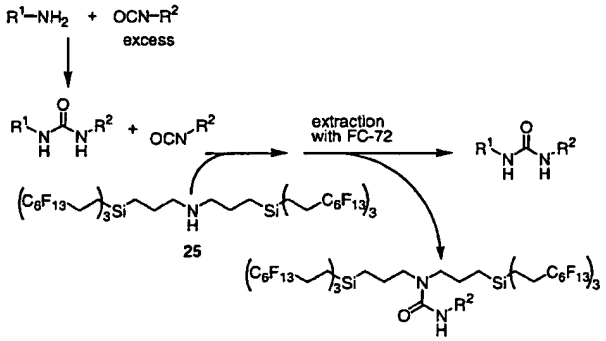


Scheme 19. The partitioning of **23** between CH_2Cl_2 and perfluorohexane is reversed upon addition of **24**.

compounds. The utility as a reagent was demonstrated by dehydration of urea to the corresponding carbodiimide and its subsequent employment as a condensation reagent for the formation of peptide and ester bonds. The urea by-product was removed by extraction with perfluoroheptanoic acid in perfluorohexane, whereas dialkyl ureas formed by conventional carbodiimide reagents are notoriously difficult to remove. The advantage of this strategy is that the reagent itself shows appreciable partitioning into the organic phase, which in turn results in respectable reaction rates. Only upon addition of the perfluoroalkanoic acid scavenger is the partitioning coefficient reversed.[131]

The application of perfluoro-tagged triphenylphosphanes to Wittig olefinations was suggested initially by Horváth and Rábai.[60] The realization of this idea in the synthesis of substituted ethyl cinnamates and cinnamic nitriles was recently reported.[132] Similarly, perfluoro-tagged triphenylphosphanes, solid-phase-bound phosphane, and triphenylphosphane were compared in an aza-Wittig reaction to give 3*H*-quinazolin-4-ones.[133]

A sulfoxide with a short fluorous tag was employed in Swern oxidations. This reagent is soluble in CH_2Cl_2 and it was removed from the crude product by continuous extraction with FC-72.[134] A perfluoro-tagged binol derivative was employed in the enantioselective protonation of a samarium enolate. The chiral proton source was recovered and could be reused several times.[135] Amine **25** was used to scavenge excess isocyanate from an automated synthesis of a library of ureas (Scheme 20). The product was obtained in high purity after removal of the fluorous urea by extraction with FC-72.[136] Polymers soluble in fluorous solvents efficiently sequester iron ions from organic solvents. Analogous water-soluble polymers have been used to remove trace metals from aqueous solutions.[137]



Scheme 20. Application of **25** as an isocyanate scavenger in the synthesis of ureas.

2.2.4. *Perfluoro-Tagged Products*

A fluorous label can also be attached to the substrate itself which renders the product soluble in fluorous solvents. Thus, this approach offers an opportunity for easy isolation and makes it particularly attractive for parallel synthesis of compound libraries. After extraction, only the labeled product is found in the fluorous phase, whereas all the other organic compounds remain in the organic phase. As an alternative to liquid–liquid extraction, the reaction mixture can be absorbed on FRPSG (Figure 3). The organic compounds are eluted with a polar organic solvent (methanol/water, acetonitrile/water), while more fluorophilic solvents (diethyl ether, perfluoroalkanes) elute the perfluoro-tagged product.[73] This strategy is conceptually similar to solid-phase synthesis, but offers distinct advantages: 1) The fluorous-tagged substances can be characterized by NMR spectroscopy, 2) reactions can be followed by thin-layer chromatography or HPLC,and 3) homogeneous reactions result in higher reaction rates.[3, 124]

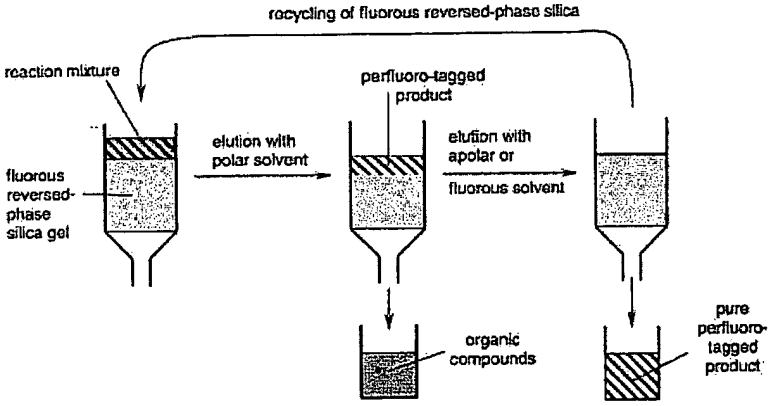
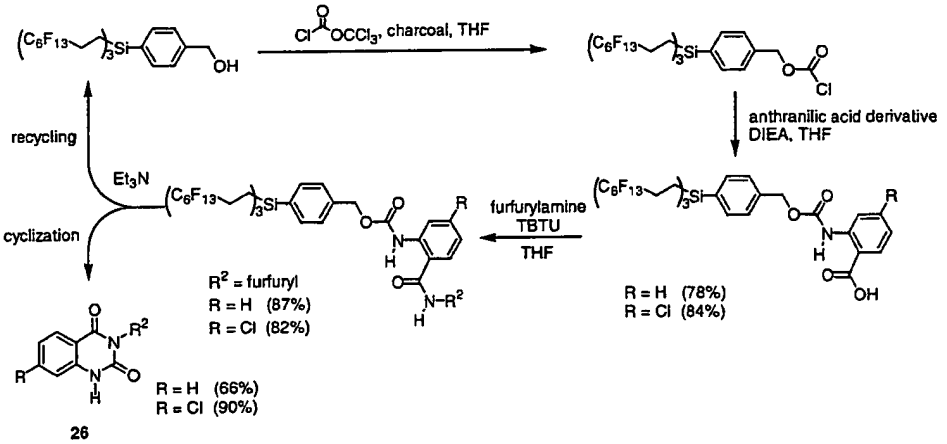


Figure 3. Separation of perfluoro-tagged compounds from organic compounds by solid-phase extraction.

While permanent labeling is necessary for catalysts or reagents, only temporary attachment of the fluorous tag to the substrate is required here (usually through the use of a modified protecting group). A perfluoro-tagged benzyloxycarbonyl protecting group was successfully used in the multistep synthesis of quinazolinediones (Scheme 21). The product was isolated after every step by liquid–liquid extraction with FC-72. Finally, quinazolinedione **26** was removed from the fluorous label by intramolecular cyclization. Since only the desired product undergoes cyclization, all incompletely converted molecules stay attached to the fluorous label and are separated from the product by extraction.[138] Fluorous labeling was employed by Theil and co-workers in the kinetic resolution of 1-phenylethanol. Lipase was used to catalyze the enantioselective esterification of the racemic alcohol with a polyfluoroalkanoic acid. Extraction with FC-72 separated the enantiomerically enriched alcohol from the ester.[139] Polyfluoroalkylsilyl groups were also employed as fluorous labels in the cycloaddition of nitriloxides to allyl silyl ether, in Ugi and Biginelli multicomponent reactions, and in the purification of Grignard products.[124, 140]

Solid-phase extraction with FRPSG is now beginning to replace liquid–liquid extraction procedures.[73] In a recent example amino acids protected by a fluorous Boc group were coupled with different amines by Curran and co-workers. The crude reaction mixtures were adsorbed on FRPSG. The organic reagents and by-products were eluted with methanol/water, the fluorous-tagged amides were eluted with methanol/diethyl ether. Alternatively, preparative HPLC over a fluorous reversed-phase column was used.[141] Preparative HPLC was used to deconvolute product mixtures coded with perfluoroalkyl chains of different length. In this approach, the synthesis is conducted with a mixture of substrates, each uniquely labeled with a perfluoroalkyl group of certain length. Upon completion of the mixture synthesis, the individual products are separated by HPLC over a fluorous reverse-phase column, with the single components eluted in order of increasing length of the fluorous tag (however, other structural features of the product also influence the order of elution). The principle was demonstrated for the synthesis of mappicine analogues and for the addition products of thiolates to acrylates.[142, 143]



Scheme 21. Use of a fluorous protecting group in the synthesis of quinazolinediones.

FRPSG was used to purify perfluoralkyl allyl compounds obtained by free-radical addition of perfluoroalkyl iodides to allyl trialkyl tin.[144] A similar synthesis of perfluoroalkylethenes was reported earlier.[145]

2.3. Supercritical Fluids

Although the discovery of the supercritical state dates back to 1822,[146] it was not until the pioneering work of Zosel[147] in 1978 that supercritical fluids (SCFs) found acceptance as solvents. They are now employed on an industrial scale for the extraction of hops, spices, flavors, perfumes, and for the decaffeination of coffee.[148, 149] In the last few years SCFs have been attracting ever increasing attention since they were found to be environmentally and toxicologically benign media for chemical reactions.[150–157] SCFs are particularly attractive in synthesis as they provide some unique properties such as high diffusion rates, enhanced heat transfer, compressibility, and the absence of gas–liquid boundaries. Their solvent properties can be easily tuned by pressure and addition of cosolvents, which provides an attractive means to influence phase behavior as well as the rate and selectivity of catalytic reactions. Product separation is fairly straightforward and essentially solvent-free products are obtained. The use of SCFs are also beneficial in different purification processes such as chromatography, crystallization, or precipitation, on both laboratory and industrial scales, thus reducing the amount of waste organic solvents significantly. However, until now extensive parallelization and automatization has been limited by the need for high-pressure equipment and by safety concerns.

2.3.1. *The Concept of Supercritical Fluids*

The critical point represents the highest pressure (p_C) and temperature (T_C) at which the vapor and liquid phases of a substance can exist in equilibrium. The distinction between gas and liquid disappears above the p_C and T_C values, and the supercritical fluid has physical properties which are intermediate between those of a liquid and a gas. The critical data for some SCFs are depicted in Figure 4.[158]

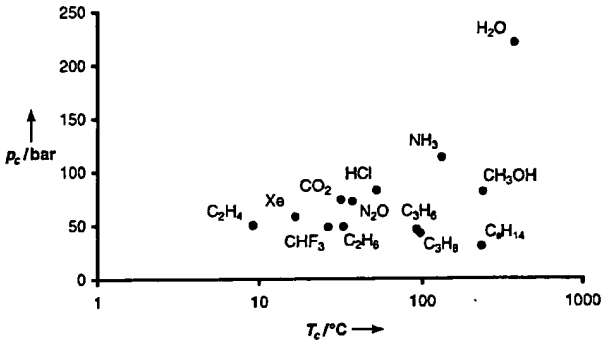


Figure 4. Critical data for some SCFs.

The properties of SCFs such as polarity, dielectric constant, viscosity, and solubility properties can vary dramatically with temperature and pressure.[159] The dielectric constant of a solvent influences chemical reactions whenever the reactants and transition state differ in polarity. The viscosity influences reactions that are diffusion-controlled or in which cage effects are important. Thus, adjusting the temperature and pressure provides a means to control reaction rates and selectivities. Furthermore, reactions can be driven to completion by precipitation of a product, and selective precipitation can be used during reaction work-up. Another important feature of SCFs is their total miscibility with gases. This observation turns SCFs into ideal media for reactions such as hydrogenation, hydroformylation, and oxidation with oxygen, where the solubility of the gaseous reagent is traditionally rate limiting.

Among the different SCFs depicted in Figure 4, $scCO_2$ and scH_2O have found widest acceptance. Supercritical water forms only a few hydrogen bonds and its dielectric constant (ε_r) is reduced from 80 to 5.[160] Hence, scH_2O is attractive for replacing organic solvents at temperatures above 200–350 °C, where it readily dissolves most organic compounds. However, the application of scH_2O is limited not only to reactants and products that are thermally stable, but also by its corrosive properties.

Carbon dioxide becomes supercritical at $T_C = 31.1$ °C and $p_C = 73.8$ bar, thus allowing for essentially mild SCF applications. Carbon dioxide is obtained as a by-product of fermentation and combustion processes. It is essentially nontoxic, nonflammable, nonprotic, and chemically inert to a wide range of reaction conditions.[161] Furthermore, $scCO_2$ has been used as a C_1-building block.[162, 163] Since $scCO_2$ is a nonpolar medium, the best solubility is observed for nonpolar solutes. The solubility of polar substances can be substantially increased by adding polar cosolvents or microemulsions.[164] Organic fluorocarbons show a particular high solubility in $scCO_2$. Numerous examples are reported in which so-called perfluoro tags have been used to solubilize substrates, reagents, and catalysts.[157, 165, 166] With $scCO_2$ and perfluorinated solvents both representing very nonpolar media, it is not surprising that their fields of application and research show a certain analogy. In fact, a number of the perfluoro-tagged reagents, ligands, and catalysts (see Section 2.2) have also been successfully tested in $scCO_2$ applications. Another synthetic SCF strategy makes use of two-phase systems, which allows for SCF transfer catalysis[167] or catalyst immobilization.[56] The combination of $scCO_2$ and ionic liquids is especially attractive (see Section 2.1.3.6).

Product isolation after a reaction in a SCF is straightforward since most SCFs, including CO_2, can be removed by simple depressurization. This is particularly useful in syntheses of thermally unstable compounds or for pharmaceutical syntheses where products have to be free of solvent residues. In analogy, high-quality crystals without any solvent molecules have been generated for X-ray diffraction studies by crystallization from a supercritical solution (CSS).[168] In contrast to conventional batch crystallization, pressure provides a second parameter in addition to temperature to trigger nucleation and growth of crystals.

There are even more elaborate separation protocols which take advantage of the tunable solvent power of SCFs. In particular, the combination of catalysis and extraction with a supercritical solution (CESS) is a new method for the recovery of homogeneous catalysts.[169–171] After venting the reactor the product is extracted from the residue with a SCF whose density is tuned to dissolve the product selectively. Thus, the catalyst remains in the reactor and can be reused. The consecutive use of $scCO_2$ and a perfluorinated solvent has been exploited in a similar strategy.[172] Finally, the rapid expansion of supercritical solutions (RESS)[173] and the supercritical antisolvent precipitation (SASP)[174, 175] processes are mentioned. Both are of relevance in pharmaceutical formulation as they allow for an effective reduction in particle size combined with a narrow size distribution.

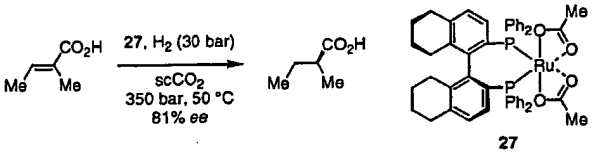
2.3.2. *Synthetic Reactions in Supercritical Fluids*

SCFs have received only a little attention as reaction media in synthetic organic chemistry. It is noteworthy, however, that a number of large-scale industrial syntheses are performed under supercritical conditions, with the Haber–Bosch synthesis of ammonia and the Fischer–Tropsch reaction, as well as polyethylene, polymethylmethacryate, and polystyrene production[176] probably being the most important ones.

2.3.2.1. *Hydrogenation*

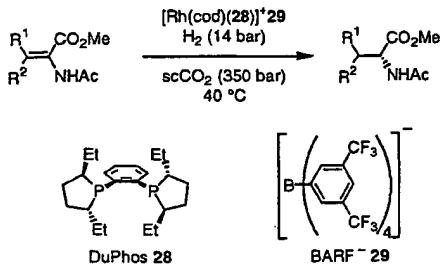
Hydrogen mass-transfer is often the rate-determining process in hydrogenation reactions. Whereas hydrogen has a rather limited solubility in most organic solvents, it is completely miscible with SCFs and turns them into ideal media for this kind of reaction. SCFs have so far been used beneficially in both homogeneous and heterogeneous hydrogenation reactions of a wide range of substrates.[177–179] Baiker and co-workers observed no increase in the enantioselectivity of a heterogeneous asymmetric hydrogenation in supercritical ethane, but observed a rate enhancement compared to the analogous reaction in toluene.[180, 181] The same effect was reported by Poliakoff and co-workers.[178, 179]

Noyori used Ru catalyst **27** containing a partially hydrogenated binap ligand for improved solubility in $scCO_2$ in homogeneous catalytic asymmetric hydrogenation reactions. The enantiomeric excess obtained was comparable to those obtained in liquid organic solvents (Scheme 22).[182] The



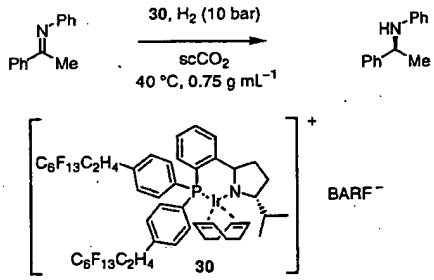
Scheme 22. Asymmetric hydrogenation using a modified Ru–binap complex.

bidendate DuPhos ligand (**28**) and the CO_2-philic $BARF^-$ counterion (**29**) were used by Tumas and co-workers (Scheme 23).[183] Asymmetric inductions obtained were comparable to those achieved in methanol or hexane. The perfluoro-tagged cationic iridium(I) complex **30** was tested as a catalyst for the enantioselective hydrogenation of

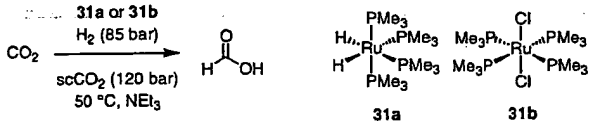


Scheme 23. Asymmetric hydrogenation using a modified Ru–DuPhos complex.

prochiral imines in $scCO_2$.[170] The highest enantioselectivities were obtained with $BARF^-$ as the counterion (Scheme 24). The hydrogenation of $scCO_2$ by soluble rhodium(II) catalysts **31a** or **31b** to yield formic acid, which could be further converted into methyl formate or *N*,*N*-dimethylformamide (Scheme 25) was also reported by Noyori and co-workers.[162, 163]



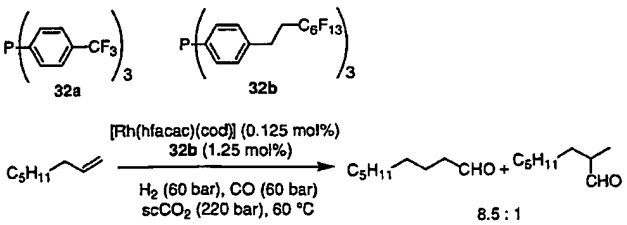
Scheme 24. Asymmetric hydrogenation of prochiral imines.



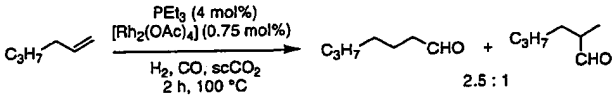
Scheme 25. Hydrogenation of carbon dioxide.

2.3.2.2. *Hydroformylation*

Hydroformylation of propene in $scCO_2$ was reported as early as 1991.[184, 185] Fluorinated phosphane ligands **32** were used by Palo and Erkey as well as Leitner and co-workers to obtain $scCO_2$-soluble rhodium(I) catalysts for hydroformylation reactions. The results obtained were comparable to those obtained in conventional systems (Scheme 26).[186–188] Similar results were found using commercially available trialkylphosphanes, which also show reasonable solubility in $scCO_2$ (Scheme 27).[189]

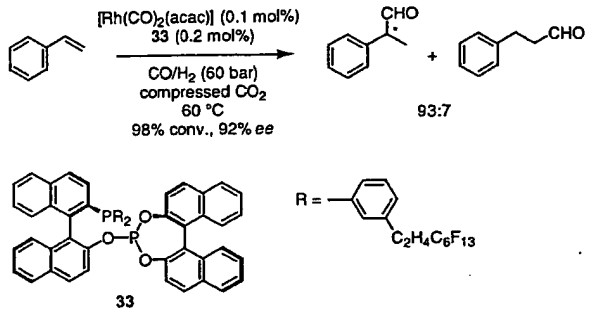


Scheme 26. Hydroformylation using **32a** and **32b**.



Scheme 27. Use of trialkylphosphanes in hydroformylation reactions.

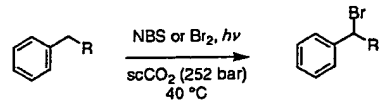
Asymmetric catalytic hydroformylation using the perfluoro-tagged (*R*,*S*)-binaphos ligand **33** and $[Rh(CO)_2(acac)]$ in dense CO_2 was addressed by Leitner and co-workers as well as by Lin and Akgerman.[169, 190, 191] The products were isolated by using a CESS procedure. The pressure was reduced to give a liquid–gaseous two-phase system, which was consequently extracted with dense CO_2, with the active catalyst left behind for subsequent reactions (Scheme 28).



Scheme 28. Asymmetric hydroformylation using a fluorinated binaphos ligand **33**.

2.3.2.3. *Halogenation*

Tanko and Blackert investigated photo-initiated bromination reactions in $scCO_2$ as a "green" alternative to halogenated solvents.[161] They found selectivities almost identical to the ones observed in chlorinated solvents. Only with molecular bromine as the brominating agent did the competing electrophilic aromatic substitution occasionally produced a small amount of a side product. This problem did not occur in the Ziegler bromination with NBS (Scheme 29).

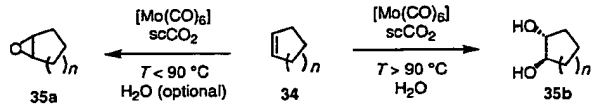


Scheme 29. Bromination in $scCO_2$.

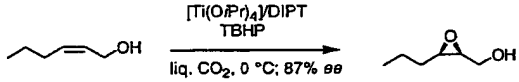
2.3.2.4. *Oxidation*[192]

As a result of their inertness towards oxidation, scH_2O and $scCO_2$ are attractive media for oxidation reactions since they provide safe processes and avoid the formation of side products from solvent oxidation. Supercritical water has found its widest and most important application in the supercritical water oxidation process (SCWO) for the total aerobic oxidation of toxic wastes.[193–196] Oxidation reactions are usually performed in $scCO_2$ and benefit from the expanded explosion limits which allow for higher oxidant/substrate ratios. Even highly exothermic oxidation processes may be controlled efficiently as $scCO_2$ shows better heat-transport capacities than gaseous mixtures.

A number of oxidation reactions in $scCO_2$ have been reported in which a metal catalyst and a TBHP oxidizing agent have been used. For example, cyclic olefins **34** could be oxidized selectively to either epoxides **35a** or *trans*-1,2-diols **35b** with $[Mo(CO)_6]$ as the catalyst (Scheme 30).[197, 198] Similarly, allylic and homoallylic alcohols have been epoxidized in liquid CO_2 using $[VO(OiPr)_3]$ as the catalyst.[198] This epoxidation reaction can also be conducted asymmetrically by employing the Sharpless procedure (Scheme 31).[198]

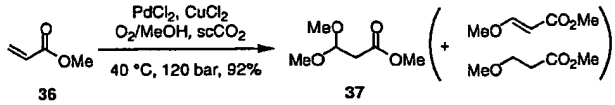


Scheme 30. Oxidation of cyclic olefins in $scCO_2$.



Scheme 31. Asymmetric Sharpless epoxidation in $scCO_2$.

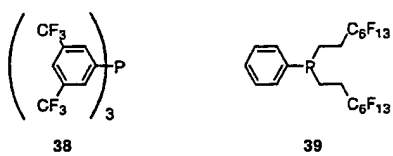
Molecular oxygen is without doubt the most attractive oxidant for selective catalytic oxidation reactions. Again, such reactions can profit from being performed in SCFs, since total miscibility with oxygen is achieved and the oxygen concentration can be easily adjusted.[199] For example, the autoxidation of substituted phenols by Schiff base complexes in $scCO_2$ gave high selectivities for the corresponding quinone at a oxygen/substrate ratio of at least 200/1, which is only practical in SCFs.[200] Scheme 32 shows an example of a palladium(II)-catalyzed oxidation of an acrylic ester **36** to dimethylacetal **37**).[201]



Scheme 32. Pd-catalyzed oxidation of acrylic ester **36** with molecular oxygen.

2.3.2.5. *C–C Coupling*

Carrol and Holmes applied the perfluoro-tagged phosphane ligand **38** for solubilization of Pd complexes and successfully employed them for Heck, Suzuki, and Sonogashira couplings in $scCO_2$.[202] Ligand **39** was shown to be

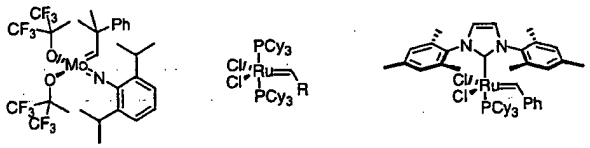


suitable for Heck and Stille couplings in $scCO_2$.[203] The two palladium complexes **17a** and **17d** were successfully tested in a Stille coupling.[172] Product purification and catalyst recycling was achieved by extracting the residue with FC-72 after dissipation of the CO_2. In both steps, the difference in solubility between $scCO_2$ and the fluorinated solvent is mediated by the perfluoro tags. The recovered catalyst was reused and showed no loss in activity.

Surprisingly, the catalyst $[Pd(PPh_3)_2]Cl_2$, which is expected not to dissolve in $scCO_2$, also mediated these Stille couplings. Recently, palladium acetate in combination with the nonfluorous ligand tris(*tert*-butyl)phosphane was also reported to give good yields in Heck and Suzuki couplings conducted in $scCO_2$.[204]

2.3.2.6. *Olefin Metathesis*

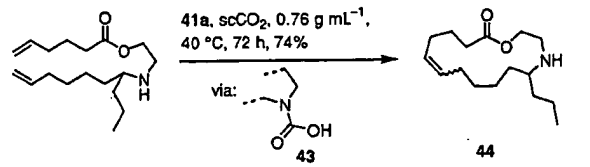
Fürstner, Leitner, and co-workers investigated ring-closing metathesis (RCM) reactions in dense CO_2. A 16-membered ring could be closed in yields of over 90% at high pressures, while mainly oligomers were obtained at lower pressures.[205, 206] This observation was explained in terms of the Ziegler–Ruggli principle, with higher pressure corresponding to a higher CO_2 density and, hence, a higher dilution. The complexes used as catalysts or catalyst precursors in $scCO_2$ are shown in structures **40**–**42**.[205, 206] While complex **40** is



40 **41a** (R = $CH{=}CPh_2$) **41b** (R = Ph) **42**

completely soluble in $scCO_2$, carbenes **41** and **42** showed no visible solubility. Isolation of the product by this process is commonly referred to as selective supercritical fluid extraction (SFE). In principle the organic materials can be collected directly from the gas stream by using appropriate traps to leave the catalyst behind.[147]

The reversible formation of a carbamic acid in $scCO_2$ from a secondary amine has been used successfully as a protecting strategy in the metathesis approach to the natural product epilachnen (**44**, Scheme 33).[205] Secondary and primary amines deactivate complex **41a** and therefore requires protection. In $scCO_2$, however, the amine is reversibly transformed into the corresponding carbamic acid **43** and good yields of the aza macrocycle **44** are obtained.[205]

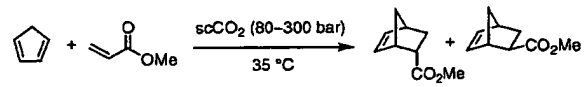


43 **44**

Scheme 33. Protecting strategy in the synthesis of epilachnen (**44**).

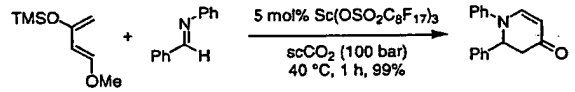
2.3.2.7. *Diels–Alder Reactions*

A significant increase in the rate constant of the cycloaddition of maleic anhydride and isoprene was observed near the critical pressure.[207–209] Furthermore, Kim and Johnston found a slight pressure dependency of the *exolendo* ratio of Diels–Alder reactions in SCFs (Scheme 34).[210] The transition states leading to the two isomeric products differ in their dipole moments. Interactions with the nonpolar solvent $scCO_2$ are pressure or density dependent, thus causing a difference in diastereoselectivity.



Scheme 34. Example of the pressure dependency of a Diels–Alder reaction.

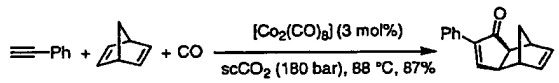
Rayner and co-workers used soluble scandium triflate for a number of Lewis acid catalyzed Diels–Alder reactions in $scCO_2$ and found improved diastereoselectivities compared to those obtained in conventional solvents.[211] For the analogous aza-Diels–Alder reactions, Kobayashi and co-workers were able to show a relationship between catalyst activity and the length of the perfluoroalkyl chains (Scheme 35).[212]



Scheme 35. Aza-Diels–Alder reaction performed in $scCO_2$.

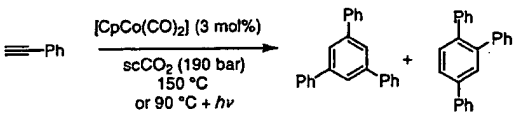
2.3.2.8. *Miscellaneous Synthetic Reactions*

Jeong et al. reported the synthesis of a substituted cyclopentenone by a Pauson–Khand reaction (Scheme 36).[213] A $[CpCo(CO)_2]$-catalyzed cyclotrimerization of alkynes in



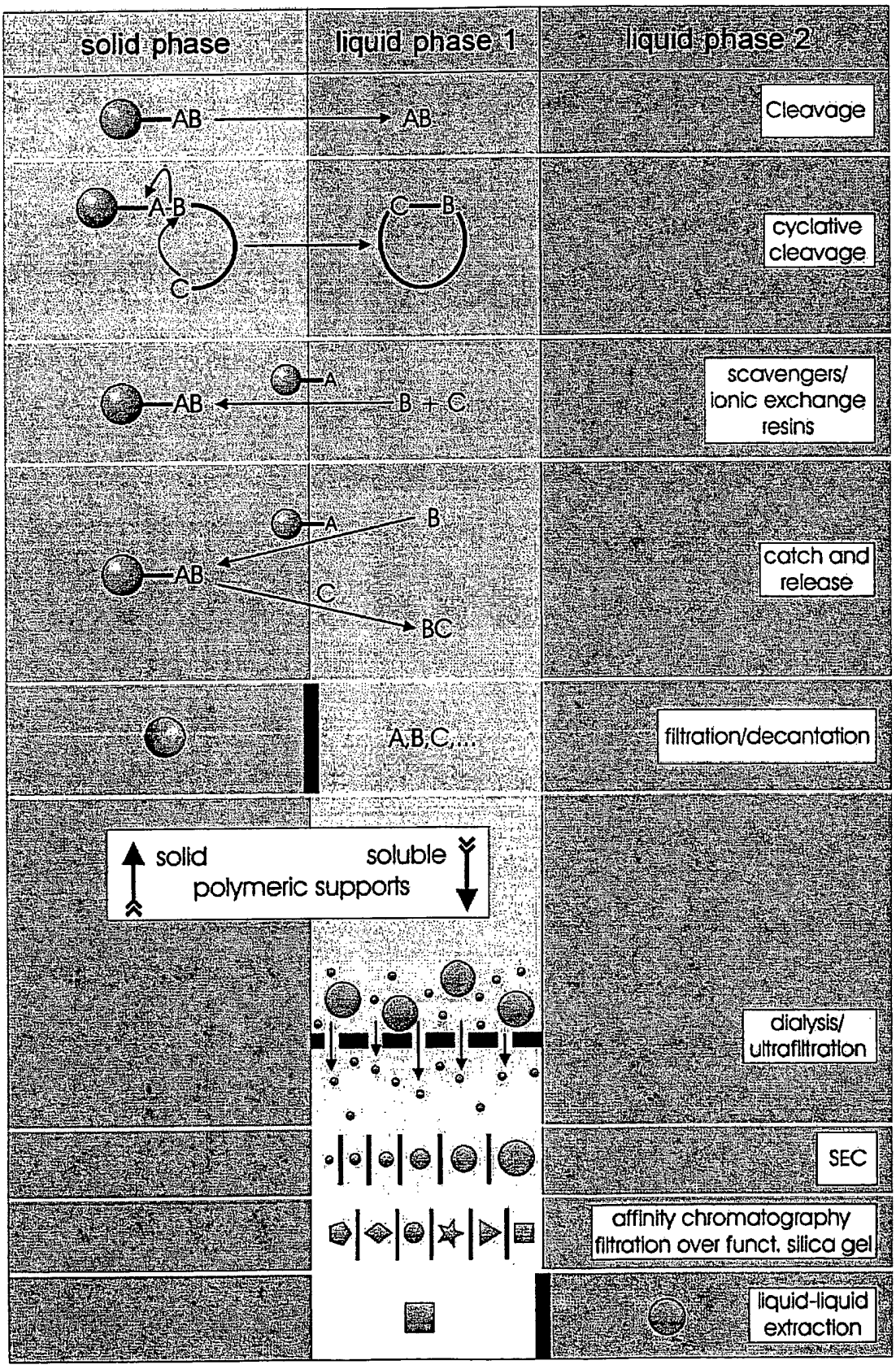
Scheme 36. Pauson–Khand reaction in $scCO_2$.

$scCO_2$ was reported by Avilés and co-workers (Scheme 37).[214] Tumas and co-workers applied an in situ generated rhodium catalyst with fluorinated trialkylphosphane ligands to hydroboration of alkenes.[215] Similarly, ruthenium- and rhodiumphosphane complexes were successfully used as catalysts for the hydrosilation of olefins in dense CO_2.[216] The great interest in utilizing SCFs for polymerization processes has been described in a series of review articles.[157, 217, 218]



Scheme 37. $[CpCo(CO)_2]$-catalyzed cyclotrimerization of alkynes in $scCO_2$.

Polymer-based separation techniques



3. Polymer-Based Separation and Purification Techniques

Polymeric supports have been used for over 50 years to simplify and accelerate the work-up of organic reactions. Initially ion-exchange resins dominated the field, while in the last decade more specific polymeric supports and linker systems have been used. A number of different polymers, cross-linked (insoluble) and non-cross-linked (soluble), have been used for many different applications.[219]

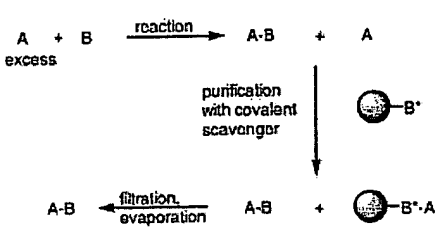
3.1. Polymer-Supported Scavenger Reagents

The ability to use multiparallel purification techniques is of great importance to solution-phase combinatorial synthesis. Polymer-supported scavenger reagents can be used since they allow for an automated purification protocol for a large number of parallel reactions.[220–224] In general, one or more solid-supported reagents which selectively bind to impurities, either covalently or ionically, are added to a reaction mixture. The choice of scavenger depends on the nature of both the impurity as well as the desired product.

This work-up procedure has frequently been performed in a parallel format. However, most of the employed scavengers have relatively small loading capacities and hence this approach is useful only for small-scale reactions. Even though the protocol can be performed by a robotic system, the automated addition of beads is still problematic. To circumvent the handling problems associated with beads, a so-called pass-flow system has recently been developed by Kirschning et al.[225] Here the beads are immobilized on a porous glass fritt sealed in a pressure tubing. This reactor can be operated by an automated HPLC system.

3.1.1. Covalent Scavengers

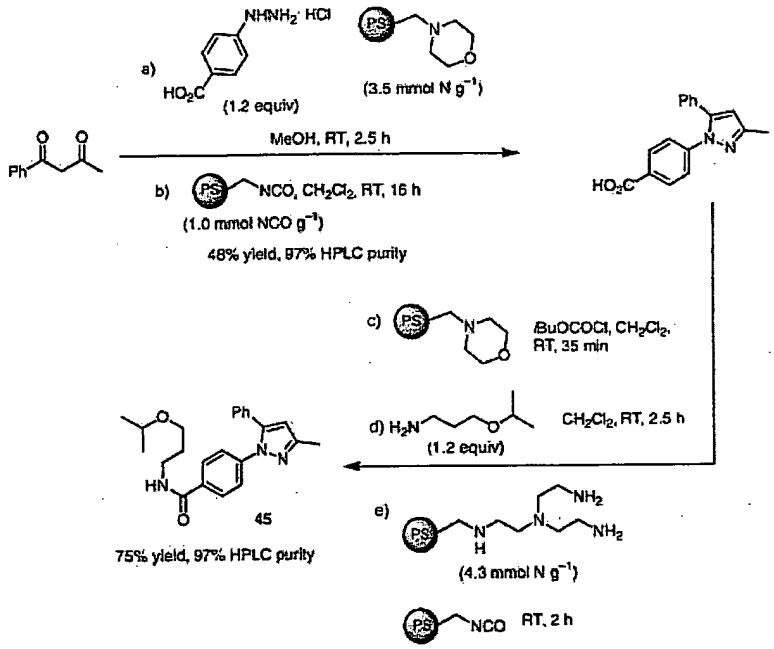
The general concept of covalent scavengers is shown in Scheme 38: Reagent **A** is present in an excess to drive the reaction to completion. The resulting reaction mixture contains the product **AB** and the remaining reagent **A**. Subsequently, the polymer-supported scavenger is added, which bears a reactive functionality **B*** that is similar to compound **B**, to consume the remaining starting material **A**. The isolation of the product is achieved by filtration and solvent evaporation.[226] Covalent scavengers have been designed for the removal of electrophiles in the presence of nucleophiles and vice versa.



Scheme 38. Schematic representation of a reaction purification with covalent scavengers.

3.1.1.1. Removal of Electrophiles by Nucleophilic Resins

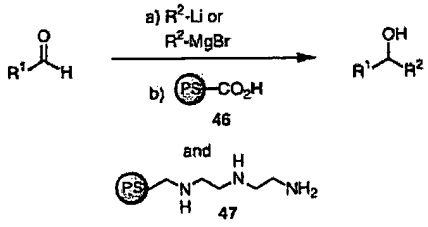
Booth and Hodges described the preparation of polystyrene-supported derivatives of tris(2-aminoethyl)amine for the scavenging of ureas, thioureas, sulfonamides, amides, and pyrazoles.[227] The multistep synthesis of a pyrazole **45** is shown in Scheme 39. In the first reaction, a polymer-bound amine is used to remove hydrochloric acid. Excess hydrazine is scavenged by a polymer-bound isocyanate. In the subsequent step the acid is activated, again in the presence of a polymer-supported base, and coupled with an amine. After this reaction, the polymer-bound amine and isocyanate are used together to remove any residual activated acid and amine. The simultaneous use of electrophilic and nucleophilic scavengers is possible, since they cannot react with each other



Scheme 39. Synthesis of pyrazole by using polymer-supported scavengers.

because they are immobilized on different beads. These resins have also been used successfully for removing acid chlorides, sulfonyl chlorides, and isothiocyanates from solutions.[228]

Aldehydes have been separated from alcohols through formation of an imine with a primary amine resin **47** (Scheme 40).[229] In this reaction a carboxylic acid resin **46**

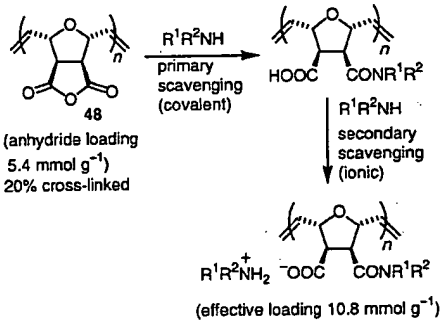


Scheme 40. Separation of aldehydes from alcohols by formation of an imine with a primary amine resin.

was used to remove any excess Grignard reagent, reprotonate the metal alkoxide, and scavenge the metal ions as salts of the resin. In another example, derivatized cellulose beads with a high loading of primary amines were used to scavenge amides and ureas.[230] In contrast to common polystyrene materials, this support can be degraded by enzymes, which could solve disposal problems.

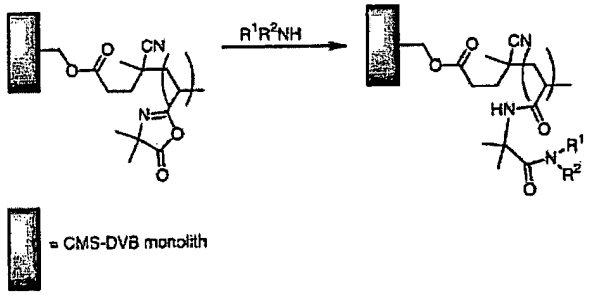
3.1.1.2. *Removal of Nucleophiles by Electrophilic Resins*

A number of resins have been developed for the removal of amines or hydrazines from solution (Scheme 39). A good choice are polymer-bound isocyanates[231] since no by-products are released from the resin during the quenching reaction. Furthermore they can be used for scavenging excess primary and secondary amines during the formation of amides and sulfonamides,[227, 232–234] as well as for the separation of secondary amines from tertiary amines and tertiary amino alcohols. Other electrophilic resins are polymer-supported aldehydes and acid chlorides.[232] Another alternative for removing excess amines and hydrazines are the so called ROMPGEL scavengers **48**, which are high-loading supported anhydrides (Scheme 41).[235]

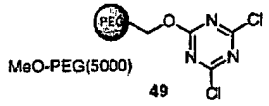


Scheme 41. Sequestration of excess amine with a ROMPGEL scavenger.

Another approach uses grafted macroporous polymer monolith disks as scavengers for amines (Scheme 42).[236, 237] These materials consist of poly(chloromethylstyrene-*co*-divinylbenzene) and are activated by graft polymerization of 4-vinyl-2,2-dimethylazlactone to its porous surface. Falchi and Taddei described polyethylene glycol–dichlorotriazine (PEG-DCT, **49**) as a soluble electrophilic scavenger.[238] It can be

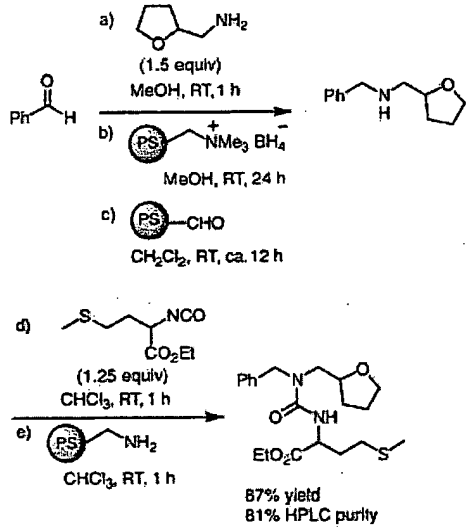


Scheme 42. Macroporous polymeric CMS-DVB monolith scavengers for the separation of amines.



obtained from reaction of trichlorotriazine with MeO-PEG-OH ($M_w = 5.000\ g\,mol^{-1}$) and can be used as a scavenger for primary, secondary, and tertiary alcohols, as well as for diols, polyalcohols (for example, D-mannitol), and for thiols in different kinds of reactions such as the formation of esters, silyl ethers, acetals, thioacetals, and thioglycosides. (For further properties and separtion techniques for soluble polymers see Section 3.4.)

The simultaneous use of both nucleophilic and electrophilic scavengers has been reported by Kaldor, Siegel et al.[232] for the alkylation and acylation of amines. Purification of the products was achieved through the use of immobilized amines, isocyanates, aldehydes, and acid chlorides. Although a complex distribution of products is obtained, purities up to 95% can be reached. Another example is shown in Scheme 43. In the first step the reductive amination requires

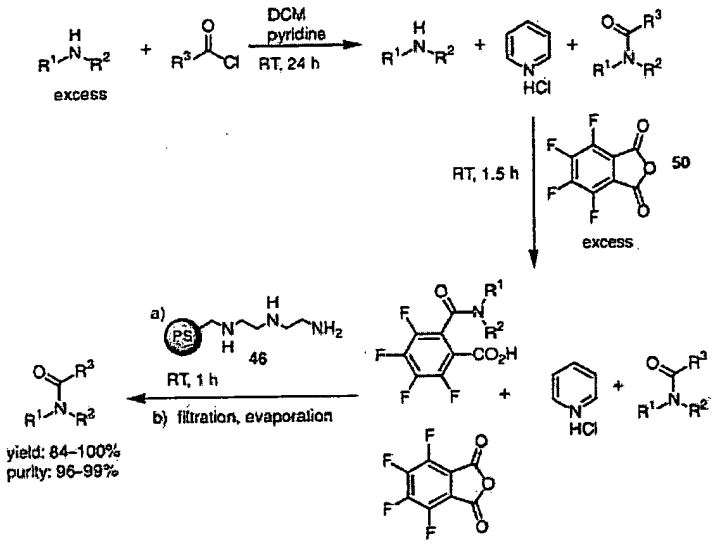


Scheme 43. Simultaneous use of electrophilic and nucleophilic scavenger resins for purification.

the use of an excess of amine to drive the imine formation to completion. Then polymer-bound borohydride is added for imine reduction and subsequently the excess of primary amine can be scavenged by a polystyrene-bound carbaldehyde. Reaction of the resulting secondary amine with excess of a functionalized isocyanate yielded the desired urea. Residual isocyanate was removed with an aminomethylated polystyrene resin.[223]

3.1.2. Purification by Sequestration-Enabling Reagent Technique

Another form of separation using covalent scavengers is the so-called sequestration-enabling (SER) technique. For example, an excess of amine in a crude product can be derivatized to a carboxylic acid by reaction with surplus tetrafluorophthalic anhydride (**50**, Scheme 44).[229] The polymeric amine scavenger **46** is then added. This reagent plays three different roles: eliminating the HCl formed during the first reaction step, thus allowing the pyridine to be removed by evaporation, and removing the hemitetrafluorophthalic acid and the excess



Scheme 44. Derivatization of excess amine with tetrafluorophthalic anhydride as a SER.

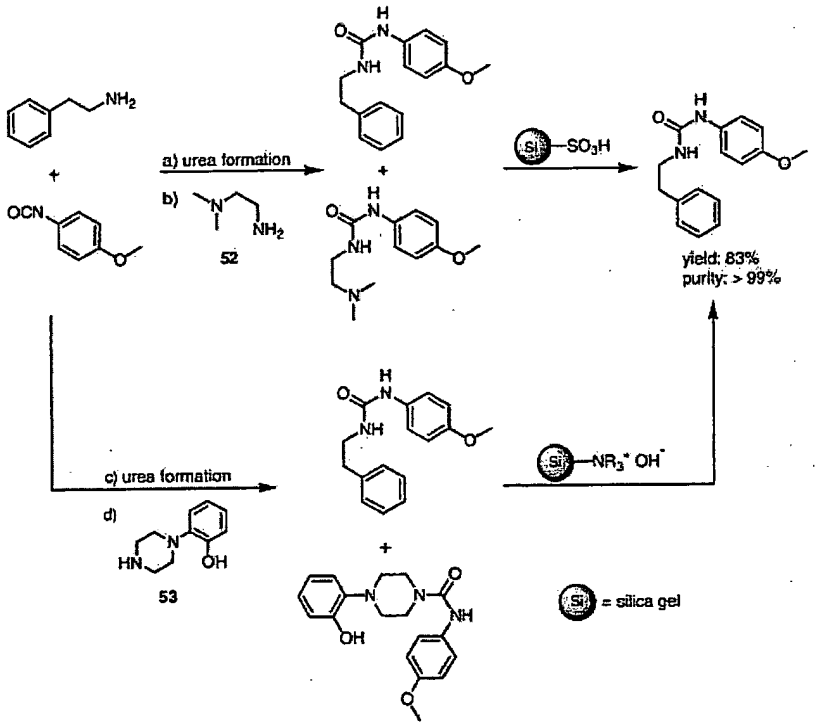
of SER reagent **50** by ionic interaction and covalent binding, respectively. This technique using electrophilic SER reagents allows for the creation of products with high purity.

A variation of the SER technique uses bis(hexafluoroisopropyl) oxalate (**51**) to form a hemiamide with an excess of amine.[239] Subsequently, the remaining active ester functionality is covalently sequestered along with excess of **51** by treatment with the polymer-bound amine **46** (Scheme 45). These SER methods are superior to the use of polymer-supported isocyanates for the removal of anilines.

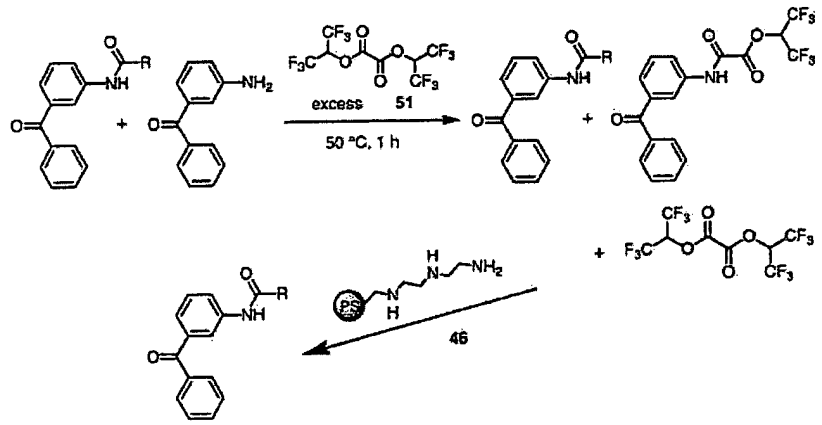
Nucleophilic SER reagents have also been described.[229, 240, 241] Scheme 46 shows an example of amine SERs **52** and **53** to remove excess isocyanate. In the case of **52**, the resulting basic compounds can be separated by cation-exchange chromatography. Alternatively, when **53** is used as the SER, the generated phenolic component is removable by anion-exchange chromatography. In general, it is often more cost-effective to perform a SER reaction so as to take advantage of a readily available and inexpensive purification resin than to spend time in developing a special scavenger resin for the same purpose.[226] The same limitations apply for parallelization and automation of the SER technique as already mentioned for polymer-supported scavenger reagents.

3.1.3. *Purification with Ion-Exchange Resins*

Polystyrene-based macroporous resins functionalized with quaternized amines and sulfonates, so-called ion-exchange resins, have been known since the 1950s and used in a wide variety of applications. Typical usages include purification of water,[242] serum analysis,[243] and protein purification.[244] In addition, they can also be used as reagents and scavengers in solid-phase organic synthesis and the purification of extremely hydrophilic molecules such as peptides and amino acids which are often difficult to purify by other methods.[245, 246] An advantage of ion-exchange chromatography over traditional methods such as HPLC or flash chromatography is that one can reliably predict the elution characteristics of a broad range of molecules solely by the presence or absence of an ionizable site in the molecule.

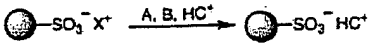


Scheme 46. Removal of excess isocyanate with a nucleophilic amine SER.



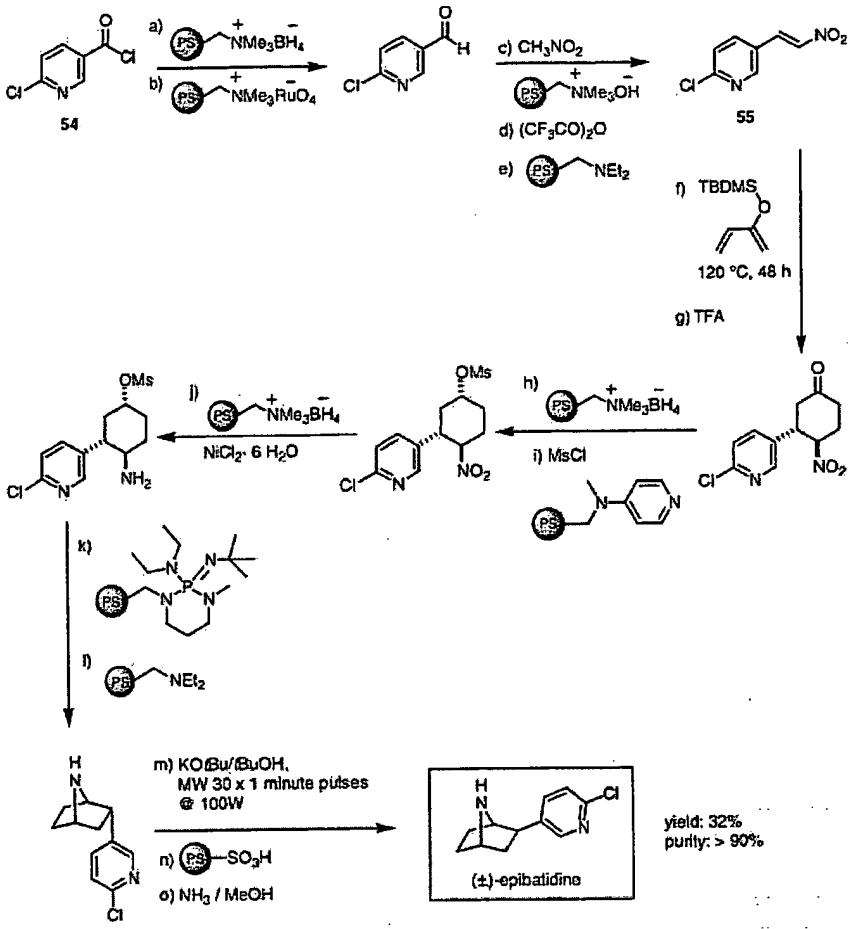
Scheme 45. Removal of amines with hexafluoroisopropyl oxalate (**51**) through formation of a hemiamide.

The typical way of using a strong cation ion exchange column is depicted in Scheme 47.[240] Two neutral molecules A and B pass through a sulfonic acid based



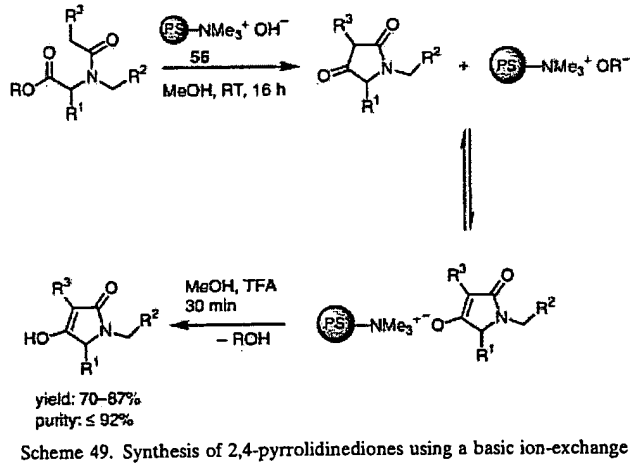
Scheme 47. Interaction with a strong cationic ion exchange resin.

cation-exchange column, while the protonated molecule C is retained. In a similar way, a cationic ion-exchange resin can be used as a scavenger for the purification of organic reactions containing, for example, amines or ammonium salts. In contrast to covalent scavenger reagents, which are mainly based on gel-type microporous PS beads with relatively moderate loading capacities (1–2 mmol g^{-1}), ion-exchange resins can have much higher loading capacities (up to 5 mmol g^{-1}). An impressive example by Ley and co-workers[247] demonstrates the high potential of scavengers in natural product synthesis, namely, the use of cation-exchange resins as scavengers in the final purification of the multistep synthesis. Scheme 48 describes the linear ten step sequence of the potent analgesic (±)-epibatidine. This compound was accessible in an overall yield of 32% and in more than 90% purity without column chromatography. This example demonstrates once more the utility of polymer-supported reagents in combination with polymer-supported scavengers for combinatorial synthesis. For example, the conversion of the acid chloride **54** to the intermediate nitroalkene **55** (five steps!) could be performed in a one-pot procedure.

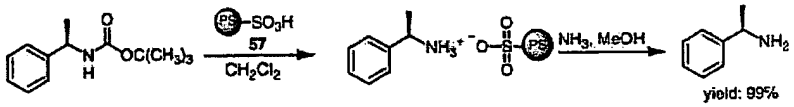


Scheme 48. Synthesis of (±)-epibatidine by using supported reagents and scavengers.

Ion-exchange resins can not only be used in purification steps but may also be included in a chemical reaction. Kulkarni and Ganesan described the application of Amberlyst A-26 (OH^- form, **56**) for effecting both ring closure and purification of libraries of 2,4-pyrrolidinediones (Scheme 49).[248] Cyclization yields the desired products as their ionically bound enolates, which were cleaved by treatment with trifluoroacetic acid. Ten compounds with yields of 70–87% and good purities of up to 92% were reported. A combination of purification and deprotection of a Boc protecting group was described by Bergbreiter, Romo, and co-workers.[249] They used an Amberlyst-15 exchange resin **57** in its SO_3^- form. As depicted in Scheme 50 the products were treated with an excess of resin **57** at room temperature in CH_2Cl_2. This process resulted in deprotection and allowed the free amino group to bind ionically to the polymeric support. By-products and impurities were subsequently washed off. Release of the primary amines were



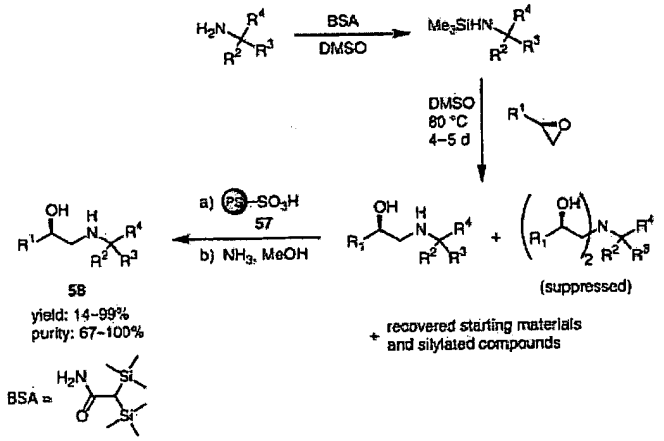
Scheme 49. Synthesis of 2,4-pyrrolidinediones using a basic ion-exchange resin.



Scheme 50. A combination of purification and deprotection with a sulfonic acid based Amberlyst-15 exchange resin.

achieved with ammonia in methanol. Ten amines were synthesized with yields of up to 99%.

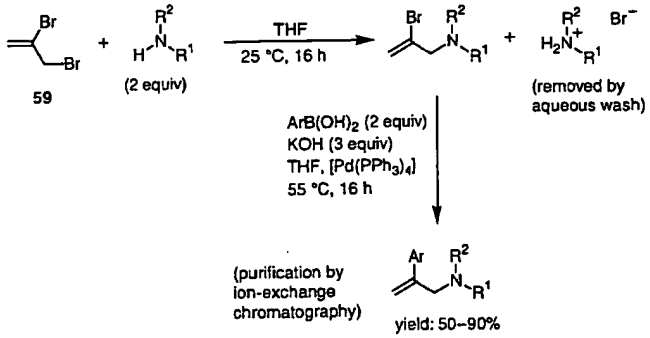
Siegel and co-workers reported the synthesis of a library of 48 β-amino alcohols **58** by using a parallel synthesis approach.[250] In the first step the primary amine is silylated in situ with bis(trimethylsilyl)acetamide (BSA) in DMSO, before adding an epoxide to the reaction mixture (Scheme 51). Isolation of the desired ethanolamine was



Scheme 51. Synthesis of a 48 compound library of β-aminoalcohols, purified by a strong ion-exchange chromatography.

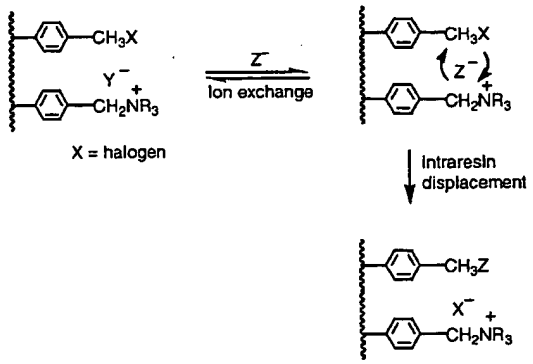
achieved using a strongly acidic ion-exchange resin **57**. The amine was retained on the column while residual epoxide, silicon by-products, and DMSO were removed by washing with methanol. Subsequently, the method was applied to an array of 8 × 6 reactions with yields up to 99% and purities up to 100%. Recently, Siegel, Organ, and co-workers described the synthesis of a 1344-member allylic amine library.[251] First, the alkylation of an excess of secondary amine with 2,3-dibromopropene (**59**) was achieved (Scheme 52). The HBr salt of the excess amine was then removed either by filtration or aqueous extraction. A subsequent Suzuki cross-coupling reaction yielded the allylamine which was purified by ion-exchange chromatography.

Another recent application of cation-exchange resins as scavengers is the removal of boronic acids from solution.[252] In this application the complexed boronic acid can be subsequently released by cyclative cleavage (see Section 3.2.1.2). Regen et al. reported on a chloromethylated polystyrene for



Scheme 52. Purification of a library of allylic amines by ion-exchange chromatography.

the scavenging of organic anions by covalent and ionic interactions.[253] Scheme 53 shows how such partially quaternized anion-exchange resins can be used. The pendant



Scheme 53. General concept using partially quaternized anion-exchange resins as covalent scavengers; X = Cl, $Y^- = Cl^-$, Z^- = cholate anion.

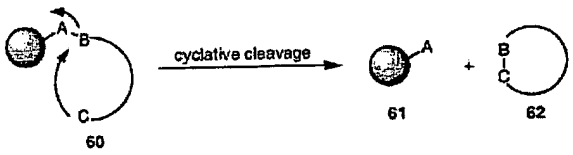
quaternary ammonium groups concentrate organic anions and therefore assist the nucleophilic displacement at the chloromethyl sites.[254–256] The ammonium groups allow for the swelling of the resin in aqueous media and thus make the chloromethyl groups accessible. Another possible way of purification is based on polymer-supported reagents. A polystyrene resin is generally used as the support and different ligands are immobilized on it. Typical ligands include amines, pyridines, imidazoles, oximes, hydroxylamines, Schiff bases, thiols, crown ethers, and a varity of phosphorus ligands.[257] This procedure thus allows a wide range of different metal ions to be recovered from solution.

3.2 Selective Cleavage from the Polymeric Support

An attractive feature of polymer-supported multistep organic synthesis is that the desired products can be selectively cleaved from the polymeric support. If a supported compound has not successfully passed every single step of the executed reaction sequence it will not be cleaved from the polymer support. Completion of a polymer-supported multistep synthesis with a selective cleavage reaction can yield products of high purity even if the previous transformations did not proceed quantitatively.[3] Thus, one of the decisive disadvantages of polymer-supported chemistry, the inability to purify polymer-bound intermediates from each other, can be overcome. Selective cleavage provides final products which ideally do not require purification, thus greatly facilitating rapid synthesis[258] and making this separation strategy ideal for parallel and automated synthesis.

3.2.1. Cyclative Cleavage

As shown in Scheme 54, cyclative cleavage is the result of an intramolecular reaction that yields a cyclized product. The polymer-bound side products are incapable of cyclizing, and thus remain attached to the polymeric support on release of the desired material.[259] Those groups which undergo intermolecular reactions during the cleavage step also remain



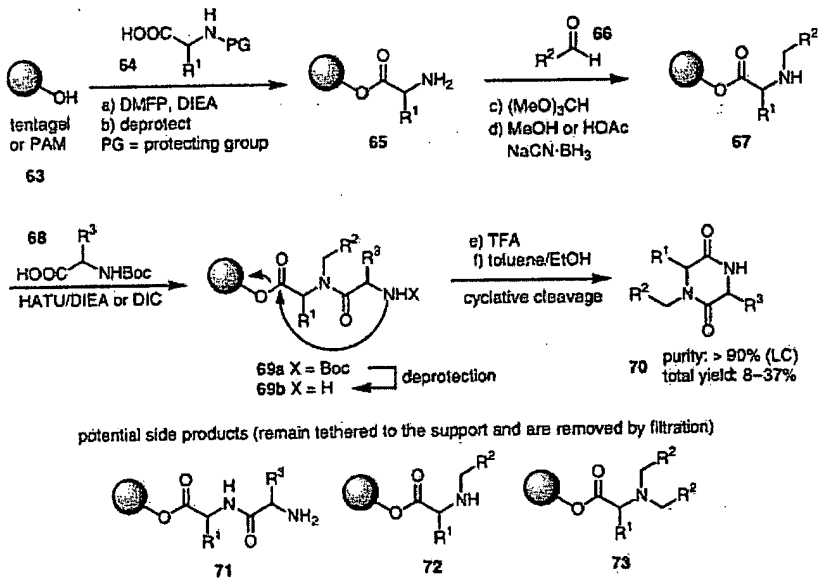
Scheme 54. The principle of cyclative cleavage.

bound to the polymeric support.[260] Cyclative cleavage often involves formation of a carbon–heteroatom bond during the cyclization step, but there are also examples of carbon–carbon bond-forming cyclizations.[261]

3.2.1.1. Cyclative Cleavage with Carbon–Heteroatom Bond Formation

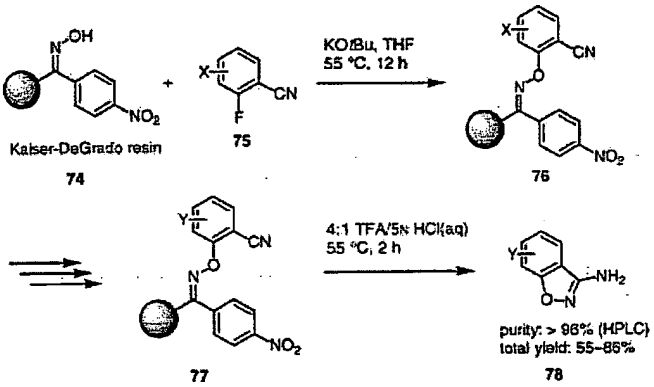
Several polymer-supported approaches to heterocycles obtained by cyclative cleavage have been described. Examples include benzazepinones,[262] benzodiazepinones,[258, 263] diazepindiones,[264–266] hydantoins,[258, 263, 267–274] thiohydantoins,[268] thiazolylhydantoins,[275] benzopyrones,[276] benzoisothiazolones,[258] benzisoxazoles,[277, 278] diketopiperazines,[265, 279–281] diketomorpholines,[280] quinazolindiones,[282, 283] hydroxyquinolinones,[284] pyrazolones,[285–287] dihydropyridines,[288] dihydropyrimidindiones,[289] pyridine-fused heterocycles,[290] oxazines,[291, 292] oxazolines,[291, 292] oxazolidinones,[293–296] phthalides,[297] lactones,[298–300] lactams,[301] cyclic sulfonamides,[302] cyclic ethers,[303–306] cyclic imides,[307] tetrahydro-β-carbolines,[308, 309] 2-quinolone,[310] coumarin,[310] indolyl diketopiperazine alkaloids,[311, 312] and cyclic peptides.[313–315] Photoinduced cyclative cleavage reactions have also been reported.[310, 316]

Diketopiperazines are quite common in nature and many natural products have been isolated with a wide range of biological activities. Szardenings et al. described two methods for the solid-phase-supported synthesis of diketopiperazines with three or four centers of diversity.[280] Each of them includes a cyclative cleavage step. The first method (Scheme 55) starts with the esterification of a protected amino acid **64**. Deprotection and reductive amination furnishs a secondary amine **67**, which is then acylated with a Boc-protected amino acid **68**. Successive deprotection results in the cyclization precursor **69b**. The cleavage-mediated cyclization yielded pure compounds **70** (>90% by LC). Potential side products, including nonalkylated **71**, nonacylated **72**, or over-alkylated **73**, remain attached to the resin and do not contaminate the library mixtures. Alternatively, these structures can also be prepared by a one-step Ugi multicomponent reaction and subsequent cyclative cleavage. Other than the building blocks, no further reagents are required, which makes this procudure especially attractive for high-throughput synthesis.



Scheme 55. Preparation of diketopiperazines.

Lepore and Wiley reported on the synthesis of 3-aminobenzisoxazoles **78** (Scheme 56).[277, 278] Several on-resin modifications such as hydrolysis and amide-bond formation, Mitsunobu reactions, nucleophilic aromatic substitutions, Suzuki reactions, Sonogashira couplings, and Horner–Wadsworth–Emmons olefinations are possible, depending on the group X. Cyclative cleavage is induced by aqueous acidic conditions.

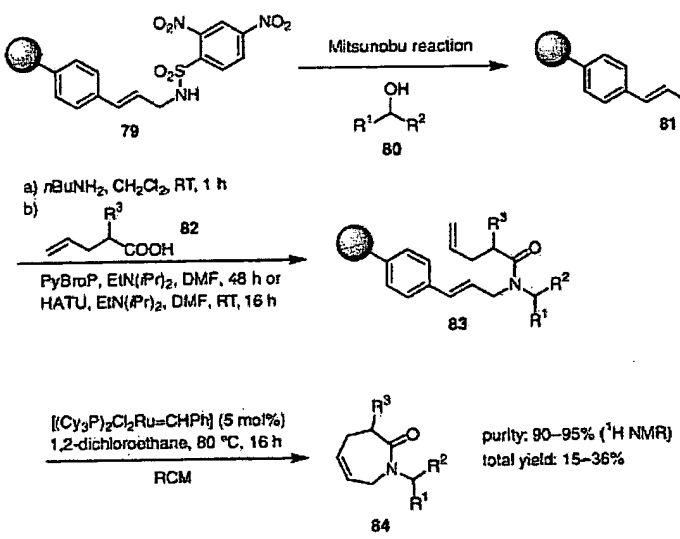


Scheme 56. Synthesis of 3-aminobenzisoxazoles.

3.2.1.2. Cyclative Cleavage with Formation of a C–C Bond

Formation of a C–C bond in the cyclative cleavage step can occur in several ways. Ring-closing metathesis has been used most frequently, for example, in the synthesis of dihydropyranes,[317] pipecolinnic acid derivatives,[317] Freidinger lactams,[317–320] and other N heterocycles,[321] furans,[322] phenols,[323] and macrocycles.[324–326] The advantages of this cyclization reaction are the chemical stability of an olefinic linker, the mild conditions required for cleavage, and the tolerance of the catalyst to a wide range of functional groups (for example, -COOH, -CONH-, -CHO, -CO-, -OH, -SONH-).[261]

Piscopio et al. described the synthesis of Freidinger lactams **84** by using an initial Mitsunobu loading step to obtain an intermediate resin-bound sulfonamide **81** (Scheme 57).[318] After cleavage of the sulfo-



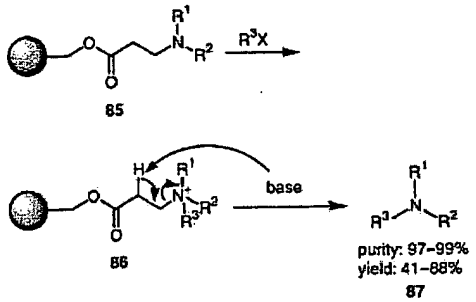
Scheme 57. Synthesis of Freidinger lactams.

namide group and acylation with an ω-unsaturated pentenoic acid derivative **82**, ring-closing metathesis with concomitant substrate cleavage provided the desired lactam **84** in high purity (90–95% by ^{1}H NMR spectroscopy). The ring-closing step can also include formation of a bond between the carbon atoms of a nucleophilic and an electrophilic. In this way, cyclic ketones,[327] tetramic acid derivatives,[328–331] indols (through the Wittig reaction),[332] and macrocycles (through the Horner–Wadsworth–Emmons reaction) have been prepared.[333] Ring closure by a transition-metal-mediated C–C coupling reaction has also been reported.[334, 335]

A cyclative cleavage based on a catch-and-release strategy was recently reported by Vaultier and co-workers.[252] In this case, a boronic acid was trapped by a cationic ion-exchange resin and subsequently released by an intramolecular Suzuki-type reaction.

3.2.2. *Noncyclative Selective Cleavage*

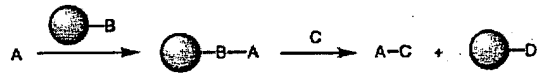
Noncyclative selective cleavage is mostly limited to selective elimination and fragmentation reactions.[303–305, 336–339] Morphy and co-workers described the synthesis of tertiary amines **87** in which a selective β-elimination cleaving step was applied (Scheme 58).[336] Coupling of the starting amine to an acrylate-functionalized polystyrene resin (Michael addition) and quaternization furnished the precursor for cleavage (**86**). Each step in the sequence has to proceed successfully for the final Hofmann elimination to occur. The purity of the final product **87** was found to be similar whether or not the individual reactions were driven to completion.



Scheme 58. Selective cleavage of a tertiary amine.

3.3. Catch-and-Release

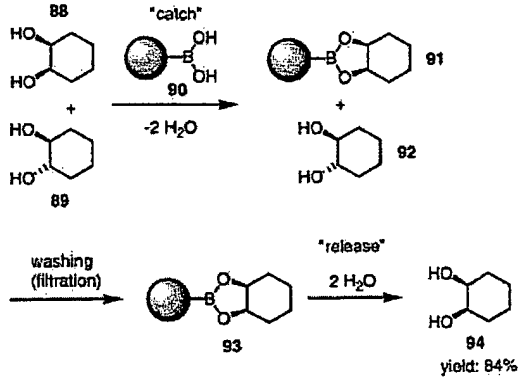
The catch-and-release strategy combines the features of both solution-phase chemistry and solid-phase chemistry. The principle of the catch-and-release strategy is shown in Scheme 59:[340] A desired low-molecular-weight compound **A** (which was synthesized in solution) is immobilized on a functionalized polymeric support to yield an activated polymer intermediate. Soluble impurities such as by-products, excess reactants, or solvent are removed by a simple filtration/washing protocol. By using this strategy merely for purification purpose, the next step will release the desired product into a new solution environment. However, it is also possible to carry out one or several modification steps on the polymer-bound compound before performing the final release step. In the latter case, catch-and-release implies a transformation to the desired compound A-C and, as such, combines solution and solid-phase synthesis.



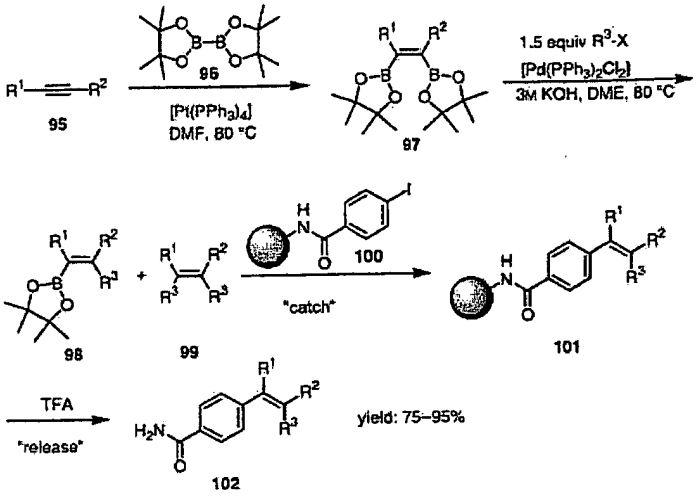
Scheme 59. The principle of the "catch-and-release" strategy.

The use of this method as a separation technique can facilitate the work-up, and is therefore particularly well-suited for multiparallel chemistry. Several applications in automated synthesis have been reported.[341–343] Since a comprehensive overview of this technique was recently published[340] we will describe only a few instructive applications.

An early example using "catch-and-release" as a purification strategy was reported by Seymour and Fréchet.[344] They separated *cis*-diol **88** from *cis/trans* mixtures using polystyrene resin **90** functionalized with boronic acid groups (Scheme 60). Brown and Armstrong used the catch-and-release strategy for



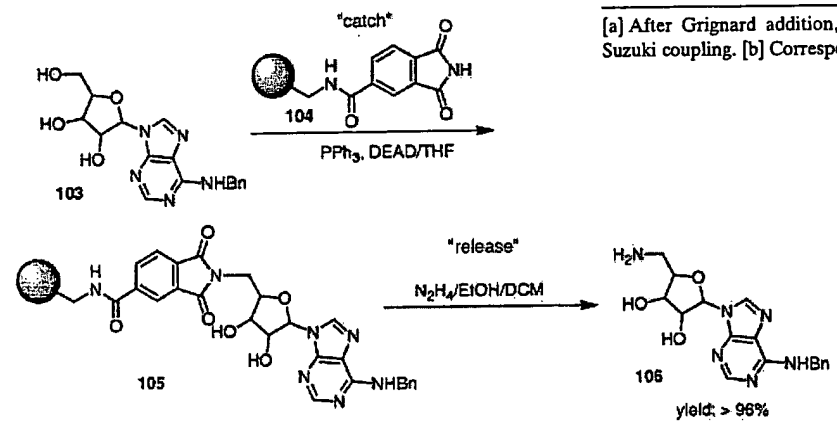
Scheme 60. Separation of *cis*-diols from a *cis/trans* mixture.



Scheme 61. Separation of Suzuki coupling products.

the separation of compounds resulting from a Suzuki coupling reaction (Scheme 61).[345] The bis(boryl)alkene **97** is transformed with 1.5 equivalents of an organo halide to give the monoaddition product **98** along with the diaddition product **99**. The mixture is combined with a resin-bound aryl iodide **100** to initiate a second Suzuki reaction. Only the monoaddition product **98** is captured on the solid support. Several coupling products **102** were obtained in high yields (75–95%) after cleavage with TFA. This route was applied to the parallel synthesis of tamoxifen derivatives.[346]

Aronov and Gelb described a procedure to "catch" alcohols and "release" amines (Scheme 62).[347] The "catch" step is realized by a Mitsunobu reaction of the alcohol **103** with a phthalimide-containing resin **104**. After washing off the soluble compounds from the resin, a hydrazinolysis "release" step releases the corresponding amine **106** in high yield (>96%) and purity. This polymer-supported phthalimide could be used for the selective conversion of less sterically hindered alcohols into corresponding primary amines or the generation of a resin-based combinatorial library starting with an alcohol. Combinations of both catch-and-release and cyclative cleavage have been employed to synthesize oxazolines, oxazines,[291, 292] and benzopyrones.[276] Table 2 gives a selection of further examples of the application of the catch-and-release strategy.



Scheme 62. Synthesis of primary amines by the catch-and-release strategy.

3.4. Purification and Separation with Soluble Polymeric Supports

It is generally believed that soluble polymeric supports are difficult to separate from the reaction mixture. However, this disregards their advantages (for example, homogeneous reaction conditions, standard analytical techniques, and high-loading capacities in some cases).

Table 2. Examples for the application of the catch-and-release strategy.

"Caught" compound	"Released" compound
acyl chlorides	amides[342]
	heterocyclic amides[387]
alcohols	alcohols (purification)[388]
	heteroatom-substituted amines, thiolates, imidazoles[a][389]
	amines[347]
	oxazines, oxazolines[291]
aldehydes	secondary and tertiary amines[391]
alkenes	alkenes (purification), alcohols[392]
alkynyl ketones	benzopyrones[276]
9-anthrylmethyl-tagged esters	methyl esters[393]
amines	amines (purification)[240, 250]
	ureas[394]
	secondary and tertiary amines[391]
	guanidines[395]
β-amino alcohols	β-amino alcohols (purification)[396]
aryl boronic acids	macroheterocycles[252]
aryl carboxylic acids	aryl amines[397]
borylalkenes	tetrasubstituted ethylenes[345, 346]
carboxylic acids	*N*-hydroxysuccinimide esters[398]
carbonyl compounds	enones
iodoalkanes	alkanes, alkenes[392]
lithioaryls	arenes
ketones	1,2,3-thiadiazoles (after Stille coupling)[341]
phenols	aryl triflates and aryl nonaflates[399]
pyridines	alkylated dihydropyridones[400]
sulfonyl chlorides	sulfonamides[342]
α,β-unsaturated carbonyls	α,β-unsaturated carbonyls (purification)[b][401]

[a] After Grignard addition, Wittig reactions, $NaBH_4$ reduction, reductive amination, Suzuki coupling. [b] Corresponding Diels–Alder adducts obtainable.[390]

Several techniques for the separation of soluble polymers from low-molecular-weight compounds have been evaluated (see Table 3).[348–351] There are various methods that separate macromolecules by size (preparative SEC, dialysis, membrane filtration and centrifugation).[352–354] All of them are suitable for automation, however, little effort has been undertaken, compared to the progress made in solid-phase synthesis, for multiparallel automation in this area. Also, other separation techniques, such as precipitation,

Table 3. Separation techniques for soluble polymeric supports.

	Dialysis[a]	Ultrafiltration[a]	SEC[a]	Precipitation/filtration[b]	Liquid-phase separation[b]
M_w of polymer [g mol^{-1}]	> 1000	> 1000	–	> 3000	–
sample volume [mL]	10–1000	1–100	< 1	1–100	10–1000
commercially available	yes	yes	yes	no	no
suitable for automation	yes	yes	yes	no	yes
suitable for high-throughput	no	yes	yes	no	yes
limitations	unsuitable for final cleavage step	–	–	unsuitable for multistep syntheses	different solubilities required

[a] Separation by differences in hydrodynamic volume; SEC = size-exclusion chromatography. [b] Separation by differences in solubility.

phase separation, and filtration through a silica cartridge have been reported. However, the application of these techniques to solution-phase synthesis depends on the physiochemical properties of each individual polymer. In addition, these techniques are sensitive to the change of functional groups on the polymeric support during the synthesis. Therefore, the use of soluble polymeric supports in combinatorial synthesis requires the careful selection of the appropriate separation technique.

3.4.1. *Separation of Soluble Polymeric Supports by Size*

For efficient and fast separations by size (hydrodynamic volume) homogenous polymeric supports should have medium molecular weights (5000–50000 g mol^{-1}) and narrow molecular weight distributions (< 1.5). In addition, macromolecules with a persistent three-dimensional structure (for example, highly branched polymers) are preferable to a linear polymer structure. Purification based on size is general, since it does not rely on other physical differences between support-bound compounds, reagents, and catalysts. However, the eluent must be carefully chosen for the individual problem.

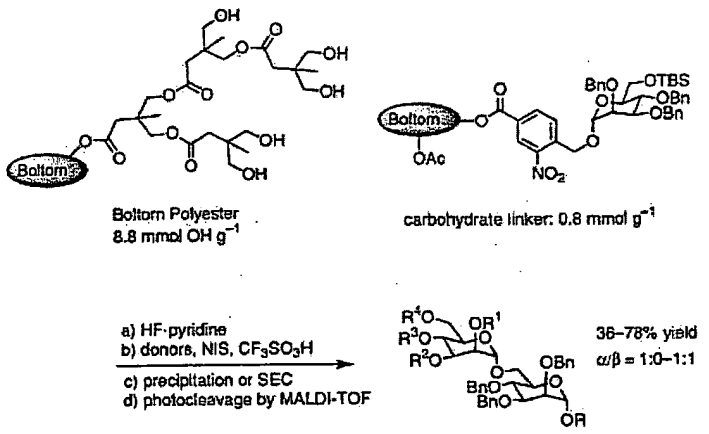
3.4.1.1. *Size-Exclusion Chromatography*

Size-exclusion chromatography (SEC; also known as gel permeation chromatography (GPC)) is used for the separation and fractionation of macromolecules on analytical and preparative scales.[350] The separation occurs predominantly by the difference in the hydrodynamic volume of the macromolecules in solution, however, in some cases the polarity of the molecules can also influence the retention times. The SEC technique, like HPLC, generally gives very reproducible elution times (typically of < 1 h) and hence can be used for automated synthesis. However, the high cost of an automated SEC system means it must be considered as a serial separation technique.

Nevertheless, SEC has been applied in combinatorial synthesis to the separation of dendritic high-loading polymeric supports from low-molecular-weight reaction products.[355, 356] Monodisperse polyamidoamine (PAMAM) dendrimers (generation 1) with an HMB-linker have been used to generate a small library (27 compounds) of indoles in a split-and-pool synthesis.[356] Separation was performed on a 25 mg (10 μmol) scale on a Sephadex LH-20 stationary phase to give good yields (> 90 %) for individual examples.

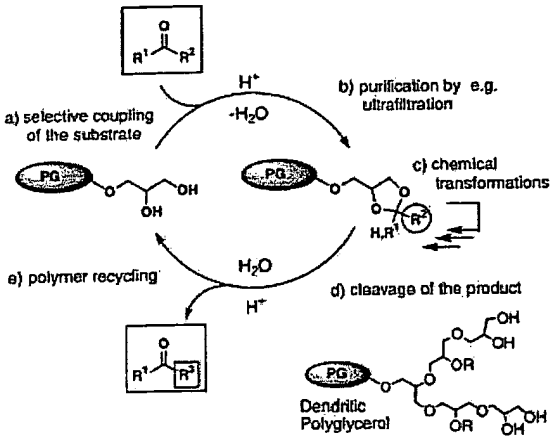
Carbosilane dendrimers (generation 0 and 1)[357] and star-like PEGs[358] have been used as multifunctional supports for the synthesis of β-lactams and guanidines, respectively. Preparative SEC was again used for the purification of the lactam and guanidine products, however, it was noted[357] that the application of membrane technology (see Section 3.4.1.2) could make an improvement. Another example of the use of SEC is the purification of dendrimer-bound salen ligands, which where employed in the enantioselective opening of epoxides.[359]

Most synthetic applications do not require the use of monodisperse polymeric supports (that is, perfect dendrimers) as long as the molecular-weight distribution of the polymer is narrow (< 1.5).[348] For example, dendritic aliphatic polyesters and polyethers have been used for the parallel syntheses of disaccharides (Scheme 63)[355] and functional



Scheme 63. Synthesis of disaccharides using a dendritic polyester support and SEC purification. In all cases thioglycoside donors were employed.

carbonyl compounds (Scheme 64),[360] respectively. In the case of the dendritic polyesters, separation was performed by SEC on a 50 mg scale, and high purities (> 90 %) and moderate yields (40–60 %) were obtained. MALDI-TOF analysis of the reaction products could be directly performed on the polyester support by using a photolabile linker. A general problem of polyester supports, however, is their limited chemical stability for a general application in organic synthesis. Although the separation of dendritic polyethers by SEC can be successfully performed, membrane separation techniques (dialysis and ultrafiltration) seem to be more promising with respect to parallelization and automation of the process.[360]



Scheme 64. Usage and separation of dendritic aliphatic polyethers as high-loading supports, for example, carbonyl compounds.

3.4.1.2. Dialysis

Dialysis is a fairly established technique for the purification of soluble polymers.[354] Originally, dialysis was mainly used for the separation of biopolymers in aqueous media because of the incompatibility of the membrane materials with organic solvents. Nowadays, however, dialysis can be performed in nearly any organic solvent as a result of improved membrane materials. Typical molecular weight cut-offs (MWCO) are 1000, 5000, and 20000 $g\,mol^{-1}$ (based on linear polymer standards in water). In organic solvents, however, the MWCO can slightly vary because of the different swelling ability of the membrane materials in different solvents.

Recently, Haag et al. introduced dialysis as a multiparallel separation technique for soluble polymers on a multigram scale (Figure 5 a, b).[360] In this way, dendritic polyglycerol,[361] a chemically stable, high-loading, soluble polymeric support, can be separated from low-molecular-weight impurities in multistep reactions. A fundamental advantage of this technique is the separation of large quantities (up to 10 mmol of substrate) in multiparallel approaches. Hence this material is attractive for the preparation of smaller libraries (10–100 compounds) on a relatively large scale. The limitations of this technique are the relatively long separation times (typically 12–36 h) and in some cases incompatibility with membrane materials, for example, for the separation of highly reactive or ionic compounds. Dialysis is also unsuitable for the final cleavage step of a multistep polymer-supported synthesis because the cleaved low-molecular-weight compound would be diluted into a large amount of solvent when diffusing through the membrane. In this case, ultrafiltration (see Section 3.4.1.3) can be used advantageously.

3.4.1.3. Ultrafiltration

A very efficient membrane separation technique for soluble macromolecules is ultrafiltration (UF), which was originally introduced by Bayer and co-workers for the automated synthesis of peptides in solution.[362] Like dialysis, it can be employed for the separation of low-molecular-weight compounds from soluble polymeric supports. Membrane materials (organic and inorganic) with high chemical stability and

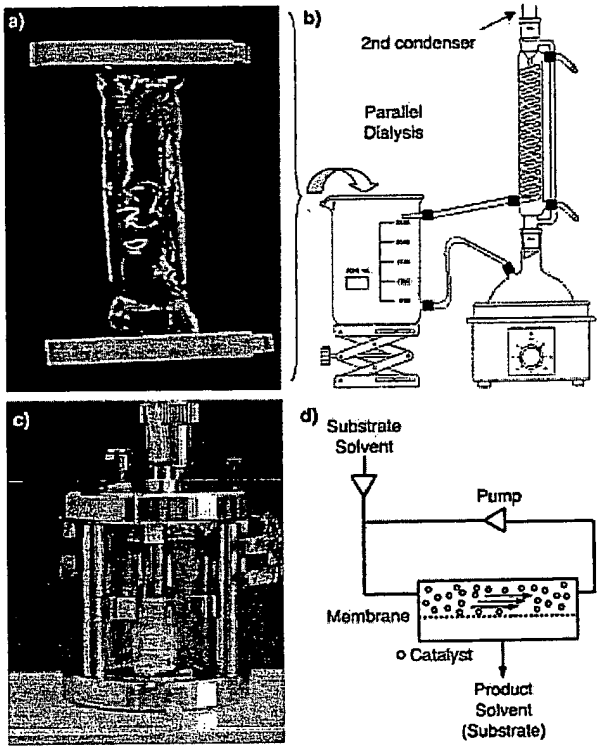


Figure 5. a) Dialysis tubing for the separation of soluble polymeric supports on a millimolar scale, b) apparatus for parallel dialysis for up to 12 reaction mixtures, c) chemically resistant UF unit for pressures up to 6 bar, d) continous flow setup for a membrane reactor (with kind permission from Dr. S. Mecking).

compatibility to most organic solvents are now commercially available.[363] In contrast to dialysis, much shorter separation times (ca. 1–3 h) can be achieved with UF because of the application of pressure (3–30 bar). It is necessary to use stirred UF cells or continuous flow systems for efficient separations to avoid clogging of the membrane. A chemically stable and commercially available set-up for pressures up to 6 bar is shown in Figure 5 c.[364] For higher pressures and continuous flow membrane reactors, however, it is necessary to use HPLC-type systems to avoid gas bubbles in the system (Figure 5 d). As a result of the high costs of the automated systems, UF must be considered as a serial separation technique.

Ultrafiltration has been used for the separation of polymeric supports during multistep syntheses as well as for the separation of products after the final cleavage step (Scheme 64).[348, 360] However, this technique is employed most frequently for the separation of polymer-supported catalysts.[352] In this case, continuous flow UF systems (so-called membrane reactors) have been used for homogeneous catalysis. In these cases, the catalysts are complexed to amphiphilic dendritic macromolecules[365, 366] or attached covalently through ligands to dendritic macromolecules.[367–371] Although UF was originally introduced for the separation of linear polymeric supports, dendritic polymeric supports have been employed in many recent applications. Oxazaborolidine-functionalized microgels have also been used as homogeneous catalysts in enantioselective reduction of prochiral ketones and separated by UF.[372]

3.4.1.4. Centrifugation

Centrifugation can also be used to generate the required "pressure" for ultrafiltration and is frequently used in biochemistry in multiparallel approaches for purification of biopolymers (for example, proteins, DNA).[373] A major drawback of this technique, however, is the limited availability of membrane vials which are stable towards a broad range of organic solvents. Also, for analytical purposes, ultracentrifugation can directly separate large molecules from small molecules, similar to SEC. In both cases the separation times depend on the rotation speed of the centrifuge.[373]

3.4.2. Separation of Soluble Polymeric Supports Based on Physiochemical Properties

3.4.2.1. Precipitation/Filtration

Other separation techniques for soluble polymers, such as precipitation/filtration and liquid–liquid phase separation, rely on polymer properties (for example, solubility) rather than their hydrodynamic volume. Precipitation is frequently used in polymer chemistry to purify the respective polymer from low-molecular-weight impurities. This method works especially well when the polymer is crystalline and the glass transition temperature is above room temperature. It has been frequently applied to the separation of functionalized PEG and non-cross-linked PS supports.[349] Precipitation, however, is less suitable for multistep syntheses because impurities often remain trapped in the precipitated polymer. In addition, large solvent volumes are required to perform quantitative precipitation and hence automation of the process is difficult.

3.4.2.2. Liquid–Liquid-Phase Separation of Polymers

Another simple separation technique which is suitable for the separation of organic molecules from water-soluble polymers is based on liquid–liquid-phase separation between an organic phase (which contains the cleaved organic product) and an aqueous phase (containing the water soluble polymer).[348, 360] Bergbreiter also used these biphasic systems for the recovery of polymer-supported catalysts.[374] Although phase separation can be performed by a robot in a serial fashion, it is limited to systems in which the components have different solubilities in the two phases. Further examples of biphasic systems for simple separation (ionic liquids, fluorous phases, and supercritical fluids) are discussed in Section 2.

3.4.2.3. Column Filtration for Separation of Soluble Polymeric Supports

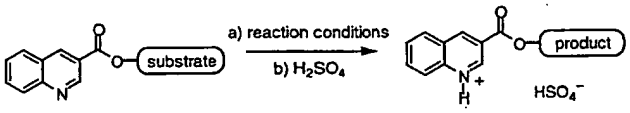
Although column filtration does not offer any advantages over conventional work-up protocols, filtration through a small amount of silica is often used as an additional purification step after the final cleavage of the product from the polymeric support. It also has been used for the separation of polymer-supported reagents from low-molecular-weight unpolar products.[375]

4. Miscellaneous Separation Techniques

The techniques mentioned in the following section are rather specific and so far have only been described for a limited number of examples. Many of them are restricted to certain functionalities or can be used only under special reaction conditions. The potential of these techniques to be automated has not yet been explored.

4.1. Phase Switch

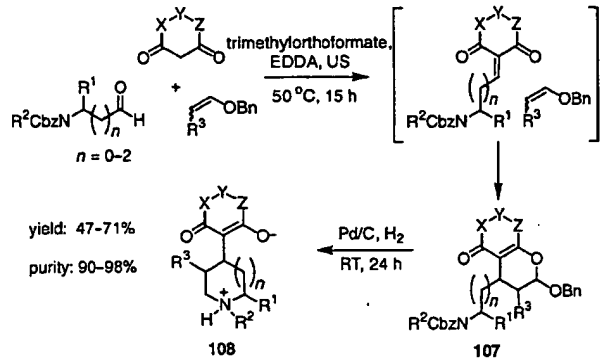
Phase-switchable tags can be used to precipitate a product from organic solutions either through salt formation[376, 377] or by configurational change (for example, *cis/trans* isomerization).[378, 379] Perrier and Labelle described a simple solution-phase/solid-phase work-up protocol in which a phase-switchable tag was employed.[377] They covalently linked a substrate to a quinoline derivative, which is soluble in many organic solvents (Scheme 65). However, the conjugate can be precipitated after each reaction step in good yield (68–91%) by



Scheme 65. Application of a quinoline tag for phase switching.

protonation to the corresponding quinolinium salt. Cleavage of the quinoline after the final reaction step, followed by precipitation liberates the desired products in high purities (>95%). In many cases the quinoline derivative was sufficiently pure for reuse in the next synthesis. Several benzylic alcohols and aromatic carboxylates have been prepared by this approach as individual compounds and also as mixtures. This purification strategy, however, might be limited by incomplete reactions, which result in mixtures of quinoline derivatives.

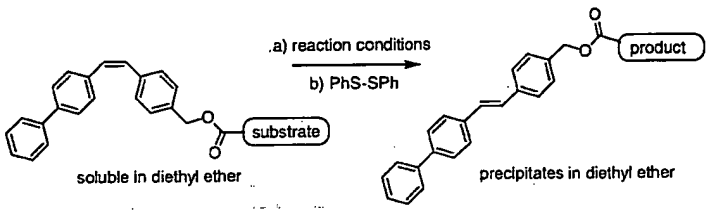
A very elegant phase-switch approach was recently described by Tietze et al. for the preparation of pyrrolidine, piperidine, and azepan derivatives.[376] In this case, the formation of a zwitterionic compound induces precipitation after a multicomponent domino reaction (Scheme 66). Sev-



Scheme 66. Synthesis of pyrrolidine, piperidine, and azepan derivatives as betains..

eral functionalized bicyclic compounds **107** can be formed from aminoaldehydes, 1,3-dicarbonyl compounds, and enol ethers through a Knoevenagel condensation and a hetero-Diels–Alder reaction. After hydrogenolytic cleavage of the protective groups and subsequent reductive amination, the corresponding betaines **108** are obtained in good yields (47–71%) and high purities (90–98%) as mixtures of diastereomers. The products are readily soluble in water and methanol and can easily be precipitated by the addition of diethyl ether. Although this approach is limited to betain formation, it does not require any coupling or cleavage of a phase-switchable tag, and hence saves time and synthetic effort.

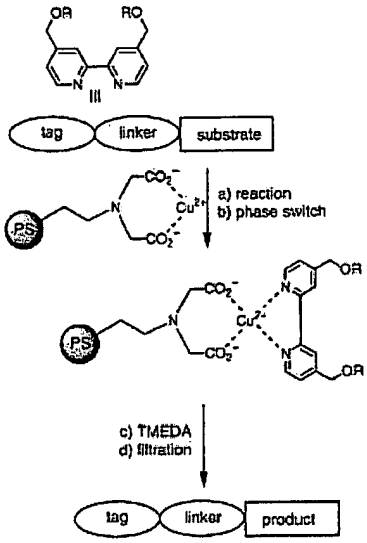
A rather unconventional phase-switchable tag was recently designed by Wilcox and co-workers.[378, 379] In this case, *cis/trans* isomerization of a stilbene derivative was used to induce precipitation from the reaction mixture (Scheme 67). 4-Phenylstilbene was chosen as the phase-switchable tag because the *cis* isomer is readily soluble in many organic solvents, while the *trans* isomer can be precipitated with, for example, diethyl ether or methanol. The isomerization can be induced either photolytically or by addition of diphenyldisulfide. A small library of isoxazolines was prepared in high yields (73–90%) and high purities (88–95%) by this approach.



Scheme 67. Stilbene tags for phase switching by *cis/trans* isomerization.

Recently, Ley et al. introduced a solid-phase Cu complex as a scavenger for dipyridyl tags (Scheme 68).[380] This method is related to metallochelate chromatography in biochemistry in which $(His)_6$ tags, which are isolated by stationary Ni complexes bound to a dicarboxylate resin, are used.[373] The commercially available iminoacetic acid resin is first used to immobilize copper salts. This solid-phase Cu complex can now be used as a phase switch for the bipyridyl derivatives. Cleavage from the resin is easily induced in excellent yields (92–95%) and high purities (>90%) with TMEDA. The broad utility of this approach was demonstrated in the synthesis of hydantoine and benzodiazepine derivatives.

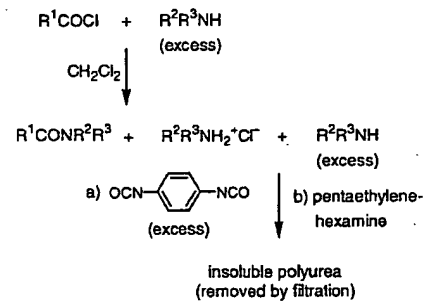
Although all these phase-switchable-tag protocols seem rather complicated they allow for reactions to be performed under homogenous conditions with monitoring by standard methods, as well as in concentrated solutions on a large or small scale.



Scheme 68. Solid-phase bound Cu complex as a phase switch for bipyridyl tags.

4.2. Purification through In Situ Polymerization

Another purification strategy is the removal of excess reagent by polymerization. A recent example of the removal of secondary amines from the reaction mixture was presented by Barrett et al.[381] Six simple amines were converted into the corresponding 3,5-dichlorobenzoic amides in high yields (85–96%) and purities (92–99%, Scheme 69). The excess amine was removed by subsequent addition of 1,4-phenylene diisocyanate (excess) and the cross-linking agent pentaethylenehexamine. The insoluble polyurea can then be filtered off and the product isolated.



Scheme 69. Removal from impurities by in situ polymerization.

4.3. Nanofiltration

While ultrafiltration (see Section 3.4.1.3) typically requires particle sizes above 1 nm, nanofiltration can separate even smaller species. Vankelecom and co-workers described a simple approach in which Ru and Rh catalysts with bulky binap-type ligands ($M_w > 300\ g\,mol^{-1}$) were separated directly with a nanofiltration membrane in a continuous system.[382] They obtained very high turnover frequencies and *ee* values for the hydration of unsaturated carbonyl compounds. Although the system is limited by the working conditions, such as solvent, temperature, and pressure, it can be applied to a number of catalysts and substrates, especially in the field of fine-chemical synthesis.

4.4. Magnetic Bead Separation

Magnetic particles that have been encapsulated within highly cross-linked polystyrene beads and then functionalized with, for example, antibodies have found various applications in the area of immunodiagnostics.[383] The use of magnetic separation in the field of solid-phase organic synthesis has been limited because of the instability and/or relatively poor loading capacities exhibited by the currently available paramagnetic supports.[384] Recently, Sucholeiki and Perez[385] as well as Bradley and co-workers[386] independently presented an approach for the preparation of higher loading (up to 1 mmol g^{-1}) magnetic solid-phase beads. The composite beads were found to compare favorably with the standard Merrifield resin under typical chemical conditions in organic solvents. These materials were used as scavengers in the synthesis of sulfonamides and tetrapeptides.[385, 386]

5. Summary and Outlook

The separation techniques presented in this review illustrate alternatives for the traditional methods, such as cristallization, distillation, and column chromatography. While solid-phase chemistry has successfully demonstrated that it can be employed for the high-throughput synthesis and purification of large compound libraries on a small scale, it has several limitations. Thus, the various solution-phase techniques available should be reconsidered. This shift in paradigm is also observed in the pharmaceutical industry, which has partially returned to the solution-phase synthesis of individual compounds in a parallel format. In addition, sustainability (recycling of the support, catalyst, etc.), which was almost forgotten in the area of solid-phase chemistry, has become increasingly important.

Also, there are great industrial efforts towards a "green chemistry". Consequently, maximum efficiency of all resources and minimum environmental impact are crucial features for all future chemical processes. Ionic liquids are among the few reaction media which could contribute to reaching these goals by replacing volatile organic solvents, minimizing the consumption of catalyst, and enhancing the overall activity and selectivity of chemical processes. Although there is little parallelization and automation in this area yet, the work-up protocols are simple enough to fulfill the requirements.

Fluorous-phase strategies must be viewed in comparison with other phase-labeling strategies. As with any of those, fluorous biphasic systems do not provide solutions to all the conceivable problems encountered in organic synthesis. Rather they should be seen as a possible specialized solution for a specific problem.

Combinatorial chemistry might become a major application for perfluoro-tagged catalysts, reagents, and products, since they offer a quite general method for work-up. Here, it is likely that solid-phase extraction will replace liquid–liquid extraction, because a lower fluorine content in the molecule is needed and because such filtration steps are easily performed in a parallel fashion, either manually or by a robot. The widespread use of perfluorinated solvents is undesirable because of their negative long-term environmental impact. Fluorous silica gel certainly is a less problematic, easily recovered, and reusable alternative for small-scale operations. Besides combinatorial chemistry, fluorous-tagged catalysts may find application in industrial-scale operations either in fluorous biphasic systems or in synthesis in $scCO_2$. In contrast to laboratory-scale synthesis, where efficient containment and recovery of fluorous solvents can hardly be ensured, high-boiling fluorocarbons can be used in industrial processes for catalyst immobilization in closed circuit operations. Efficient quantitative recovery of fluorocarbons is imperative because of environmental concerns and the high cost of such solvents as well.

While fluorous reagents are a viable alternative in combinatorial chemistry, they are not likely to enter rapidly into the broad field of everyday synthesis, since they have to compete with established conventional reagents and a variety of solid-phase-bound reagents. Again, they might find specialized application in the commercial synthesis of fine chemicals, where their easy separation and regeneration presents a significant advantage.

One major advantage of SCF techniques over all other solution-phase techniques is the ease of product isolation. Simple depressurization suffices to obtain completely dry products if SCFs are used that are gaseous at normal pressure. This is an extremely important aspect, especially for the production of pharmaceuticals, where traces of solvents are not tolerated. Also, the tunable solvent power of SCFs allows for the development of a number of more elaborate separation schemes which are attractive for the separation from catalysts. Furthermore, $scCO_2$ has the potential to become the ideal "green solvent" which can be used to replace many potentially hazardous organic solvents. This may prove to be particular advantageous in the preparation of pharmaceuticals, cosmetics, and food additives.

In contrast to these alternative solution-phase systems, solid-phase supports have so far dominated the field of combinatorial chemistry as well as the automation of separation techniques. After ten years of intensive research, however, there is still no polymeric support for general application in combinatorial chemistry. Every polymer has its drawbacks (for example, chemical stability, polarity, loading capacity). Soluble polymeric supports have also had a similar, but less pronounced, revival over the past decade. Aliphatic polyethers and non-cross-linked polystyrene are among the most promising candidates in terms of stability. Dendritic and linear polyfunctional soluble polymers have by far the highest loading capacities and show great potential as supports for reagents and catalysts in combinatorial synthesis. Although many separation techniques for soluble polymeric supports have been developed for solution-phase organic synthesis (some, even in a parallel format), further progress in the automation of solution-phase separation techniques is required. For example, membrane stability towards all organic solvents and better size selectivity are still insufficient in the case of membrane separation (dialysis, ultrafiltration).

There are still many new developments in the field of polymer-based separation techniques, such as smart cleavage protocols and phase-switching protocols (including catch-and-

release). Even though predictions about the future impact of this area are very speculative, the number of polymeric support based separations will certainly increase tremendously.

Among the various alternative separation approaches presented, there is nothing approaching "the best method"! Instead, it is more a search for an appropriate separation technique. Each individual chemical problem can only be successfully solved if the separation technique has been well-chosen and optimized. This becomes even more important for parallel approaches where small separation problems are amplified into a whole library. In the search for new separation strategies one should always bear in mind that it has to be a general tool for achieving the synthetic goal and not vice versa.

Abbreviations

acac	acetylacetonate
BARF	tetrakis(3,5-di(trifluoromethyl)phenyl)borate
binap	2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl
binaphos	2-(diphenylphosphanyl)-1,1′-binaphthyl-2-yl-1,1′-binaphthyl-2,2′-diyl-phosphite
binol	2,2′-dihydroxy-1,1′-binaphthyl
BMIM	1-*n*-butyl-3-methylimidazolium
Boc	*tert*-butyloxycarbonyl
BSA	bis(trimethylsilyl)acetamide
CESS	catalysis and extraction using supercritical solution
CMS-DVB	poly(chloromethylstyrene-*co*-divinylbenzene)
cod	cyclooctadiene
CSS	crystallization from supercritical solution
Cy	cyclohexyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
dca	dicyanamide anion
DCT	dichlortriazene
DIC	5-(3,3-dimethyl-1-triazenyl)-1*H*-imidazole-4-carboxamide
DIEA	diisopropylethylamine
DIPT	diisopropyl tartrate
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMFP	1,3-dimethyl-2-fluoropyridinium 4-toluenesulfonate
DMSO	dimethylsulfoxide
DuPhos	1,2-bis(2,5-dimethylphospholanyl)benzene
EDDA	ethylenediammonium diacetate
ee	enantiomeric excess
EMIM	1-ethyl-3-methylimidazolium
FBC	fluorous biphasic catalysis
FBS	fluorous biphasic system
FC-72	perfluoroalkane solvent, mainly C_6H_{14}
FRPSG	perfluorous reversed-phase silica gel
GPC	gel permeation chromatography
HATU	*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate
hfacac	hexafluoroacetylacetonate
HMB	4-hydroxymethylbenzoic acid
HPLC	high pressure liquid chromatography
LC	liquid chromatography
MTO	methyl trioxorhenium
MWCO	Molecular weight cut-off
NBS	*N*-bromosuccinic imide
NMP	*N*-methylpyrrolidone
PAM	phenylacetamidomethyl
PAMAM	polyamidoamine
PEG	polyethylene glycol
PFMCH	perfluoromethylcyclohexane
PG	protecting group
PS	polystyrene
PyBroP	bromo-tris(pyrrolidine)phosphonium hexafluorophosphate
RCM	ring-closing metathesis
RESS	rapid expansion of supercritical solutions
ROMP	ring-opening methatesis polymerization
salen	*N*,*N*′-bis(2-hydroxybenzylidene)-1,2-diaminoethane
SASP	supercritical antisolvent precipitation
$scCO_2$	supercritical carbon dioxide
SCWO	supercritical water oxidation process
SEC	Size-exclusion chromatography
SER	sequestration-enabling technique
SFE	supercritical fluid extraction
TBAB	tetrabutylammonium bromide
TBHP	*tert*-butylhydroperoxide
TBME	*tert*-butyl methyl ether
TBTU	benztriazolyl-tetramethyluronium tetrafluoroborate
TEMPO	2,2,6,6-tetramethylpiperidin-*N*-oxide
TFA	trifluoroacetic acid
T_g	glass transition temperature
THF	tetrahydrofuran
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TLC	thin-layer chromatography
tolbinap	2,2′-bis(ditoluylphosphanyl)-1,1′-binaphthyl
UF	ultrafiltration
US	ultrasonication

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[1] The original meaning of "combinatorial synthesis" has partially disappeared and it is nowadays used as a synonym for (automated) synthesis of compound libraries in a parallel format.
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APPENDIX G

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Non-Covalently Solid-Phase Bound Catalysts for Organic Synthesis

J. Horn · F. Michalek · C. C. Tzschucke · W. Bannwarth (✉)

Institut für Organische Chemie und Biochemie, Albert-Ludwigs-Universität Freiburg, Albertstr. 21, 79104 Freiburg, Germany
willi.bannwarth@organik.chemie.uni-freiburg.de

Abstract Catalysts immobilized on solid supports have become valuable tools for simplified product isolation and catalyst recycling. An alternative to covalent attachment to a solid support is to immobilize catalysts by non-covalent bonding through hydrogen bridges, or ionic, hydrophobic or fluorous interactions. Compared to covalent attachment, such non-covalent approaches increase the flexibility in the choice of the support material, reaction conditions and work-up strategies. Numerous catalytic reactions employing one of these non-covalent bonding strategies have meanwhile appeared in the literature.

Keywords Supported catalysts · Non-covalent immobilization · Heterogeneous catalysis

Abbreviations

acac	Acetylacetonate
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
bmim	1-Butyl-3-methylimidazolium
CPG	Controlled-pore glass
CTAB	Cetyltrimethylammonium bromide
DME	Dimethoxyethane
ee	Enantiomeric excess
FRPSG	Fluorous reversed-phase silica gel
LDH	Layered double hydroxide
NBD	Norbornadiene
o-Tol	*ortho*-Tolyl
OTPPTS	Triphenylphosphine trisulphonate oxide trisodium salt
RPSG	Reversed-phase silica gel
RT	Room temperature
SAPC	Supported aqueous-phase catalysis
TOF	Turnover frequency
TON	Turnover number
TPPMS	Triphenylphosphine monosulphonate monosodium salt
TPPTI	Triphenylphosphine trisulphonate tris(1-butyl-3-methyl-imidazolium) salt
TPPTS	Triphenylphosphine trisulphonate trisodium salt

1 Introduction

In recent years, supported catalysts have become valuable tools for the simplified separation and recovery of catalysts from reaction mixtures. Commonly, the catalysts are attached covalently to a solid support. This covalent attachment of catalysts may lead to a partial loss of efficacy due to the decreased mobility. Alternatively, catalysts can be immobilized by non-covalent bonding through hydrogen bridges, or ionic, hydrophobic or fluorous interactions. Compared to covalent attachments, such non-covalent approaches increase the flexibility in the choice of the support material, reaction conditions and work-up strategies.

Adsorption on silica gel surfaces or silica gels coated with water or thin layers of ionic liquids has been used to immobilize transition metal complexes by ionic interactions and hydrogen bonding. Reversed-phase silica gels were used to retain catalysts by hydrophobic interactions. Support of catalysts on fluorous reversed-phase silica gel by the solvophobic nature of perfluoroalkyl chains is a new and promising approach with potential in catalysis and combinatorial chemistry.

2 Catalyst Immobilization in Polar Liquid Films on Solid Phase

2.1 Supported Aqueous-Phase Catalysis

Supported aqueous-phase catalysis (SAPC) was introduced by Davis and coworkers in 1989 as a new type of heterogeneous catalysis [1]. The key feature of the concept is to immobilize a polar (e.g. water, ethylene glycol) catalyst in a thin layer of hydrophilic liquid that is supported on a solid hydrophilic material. The support is then used for catalysis in organic solvents immiscible with the hydrophilic film, thereby retaining the catalyst on the support. Silica and controlled-pore glass (CPG) are the supports of choice because they are hydrophilic and have a high surface area. As hydrophilic liquid phase, water and ethylene glycol are used because they are immiscible with most organic solvents. The catalysts used have to be hydrophilic. Therefore, commercially available metal precursors (e.g. $PdCl_2$) are mixed with water-soluble ligands (e.g. sulphonated phosphines).

There are two methods for SAPC. In the first method, the solid support is added to a solution of the catalyst precursor and the solvent is evaporated in vacuo. Thus, the surface of the support is covered with the metal complex. Immediately before the reaction, the desired amount of water is added to the support. The second method is the so-called self-assembly method. Here, all components necessary for the SAPC including the substrates and the organic solvent are placed in the reactor. During the reaction, the supported catalyst is formed in situ.

The reactions are proposed to take place at the water–organic interface, either in the pores or on the surface of the support, depending on the pore size and the amount of hydration (Fig. 1) [2–4]. After the reaction, the heterogeneous catalyst is easily separated from the product phase by filtration or decanting. After washing of the solid phase, the catalyst can be reused. A further advantage of SAPC is that it needs no covalent attachment to the solid support, and existing catalytic aqueous–organic biphasic systems can be transferred to SAPC. Because of the features mentioned above, the SAPC principle is of great importance for economic and ecological reasons. Meanwhile, many different applications using SAPC have appeared in the literature, which are summarized in the following sections in more detail. Recently, the principle of SAPC was extended to ionic liquid films on silica gel, in which polar catalysts were immobilized.

2.1.1 C–C Coupling Reactions

One of the most versatile methods for C–C bondformation is Pd-mediated C–C coupling. These reactions are widely used on the laboratory scale as well as in industrial processes.

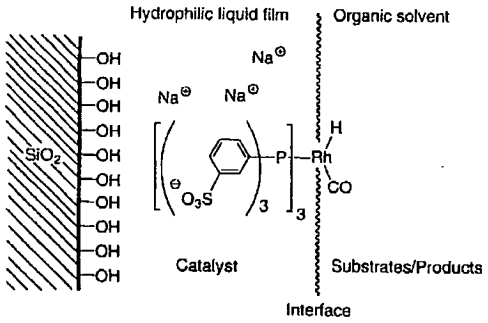
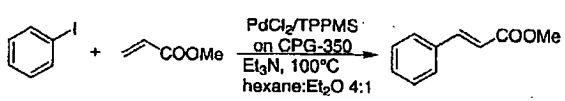


Fig. 1 Model for a SAPC catalyst

2.1.1.1 Heck Reaction

The Heck reaction of iodobenzene and methyl acrylate was successfully applied under SAPC conditions (Scheme 1) [5]. Prior to reaction, a small amount of ethylene glycol was added to the dried supported catalyst, thus forming the SAPC system. The employed ligands were the sodium and lithium salts of triphenylphosphine trisulphonate (TPPTS) and triphenylphosphine monosulphonate (TPPMS). Comparing the different ligands, it was observed that TPPTS retained the palladium better in the hydrophilic film but showed lower activity. On the other hand, the TPPMS/SAPC system was more active. However, more leaching of metal into the organic phase took place. Concerning the counter-ions, sodium turned out to be superior to lithium because its complex proved to be more actively associated with a decreased loss of palladium. From their results, the authors decided that Na-TPPMS was the best compromise between hydrophilicity, activity and leaching.

The activity of the catalyst increased linearly with the amount of supported palladium. The experiments revealed that more than 85% of the activity originated from palladium complexes dissolved in the organic phase, which indicated that the reaction proceeded predominantly homogeneously. However, most of the metal species were taken up again during the reaction. This observation was called temporary leaching. Only a small amount remained in solution after the end of the reaction. The leaching of the metal could be eliminated by adding 6.5 equivalents of TPPMS. When higher excesses of ligand were



Scheme 1 Heck reaction

used, the activity decreased by a factor of 3. Recycling experiments of the Heck/SAPC system showed a significant decrease of the activity after the first run. At the same time, high amounts of oxidized phosphine ligands (OTPPMS) were observed. It was suggested that the OTPPMS rendered the palladium inactive.

Investigating the influence of the loading of the hydrophilic liquid phase, it was observed that maximum activity was obtained with a pore filling of 10%. That amount of hydrophilic phase corresponded to a theoretical film thickness of 16 Å. Molecular modelling of the Pd-TPPMS complex revealed that the average diameter of the complex was 11 Å, the largest diameter being 15 Å. Thus, a monolayer of catalyst on the support was assumed.

CPG material was used as support instead of silica gel for a Heck/SAPC system [6]. There, iodobenzene was coupled with different olefins. The dependencies of different substrates and different bases on the activity were examined. The system was active for several types of olefins. The reactivity of the aryl halides was comparable to that of the homogeneous catalysis. Iodides reacted easily, while bromobenzene was converted inefficiently. No reaction occurred using chlorobenzene. With Et_3N as base, the highest conversions were achieved. However, leaching of palladium was observed and an *E/Z* mixture of products was isolated. When the amine was replaced by KOAc, the Heck reaction gave selectively the *E*-isomer. No leaching was observed (detection limit approx. 0.1 ppm), but the conversion dropped to 80%. The catalytic system with KOAc as base was successfully used for five consecutive runs, with an overall TON of > 1,200. In all cases, conversion ranged from 70 to 80% and 100% selectivity of the *E*-isomer was achieved.

In addition, the Heck reaction of iodobenzene with butyl acrylate was studied in more detail [7]. In all experiments, butyl cinnamate was selectively produced. It was observed that the activity was only dependent on the palladium concentration in the hydrophilic liquid, but neither on the total amount of complex applied nor on the quantity of the liquid used. In recycling experiments, a short induction period occurred in the first runs. This was not observed in the following runs. Furthermore, repeated application of the catalyst resulted in an increased reaction rate. Other investigators observed a decrease of activity during the recycling experiments [5]. The authors explained their results with an accumulation of Et_3NHI during consecutive runs. It was assumed that the accumulated ammonium salt had the same promotion effect as tetrabutylammonium halide additives in Heck reactions (Jeffery conditions) [8].

Apart from palladium, nickel is also known to catalyse Heck vinylations [9–12]. A supported nickel catalyst was applied for the Heck reaction of iodobenzene with butyl acrylate [13]. The supported aqueous-phase catalysis performed almost as well as the analogous homogeneous catalyst $NiCl_2(PPh_3)_2$. Only the conversion was slightly lower. No leaching of metal into the product phase was observed (detection limit approx. 1 ppm). The immobilized catalyst was successfully recycled three times without observing loss of activity and selectivity.

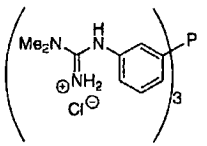


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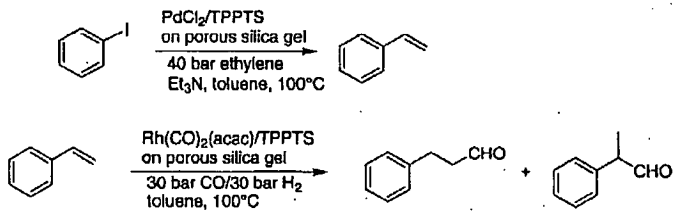
Fig. 2 Guanidinium phosphine

Besides sulphonated phosphines, guanidinium phosphines are also able to render metal complexes water-soluble. Their synthesis is straightforward in contrast to the harsh conditions required for sulphonation [14]. The guanidinium phosphine 1 (Fig. 2) was prepared in three high yielding steps [15]. Heck reactions afforded moderate to good yields (55–87%) combined with low palladium leaching (≤0.2%). Recycling experiments were successful. The coupling of iodobenzene and methyl acrylate was performed in four consecutive runs. In each run, the product was isolated in good yield (78–85%) and only a low palladium leaching was observed (≤0.2%).

Multifunctional catalytic systems reduce the number of steps for the synthesis of complex molecules. Until today, only a few reports are known of mixtures of homogeneous catalysts [16, 17]. Commonly, when different homogeneous catalysts are mixed, unfavourable interactions between the organometallic species occur, thus decreasing the activity of each catalyst. The concept of supported liquid-phase catalysis was used to overcome this problem [18]. Different immobilized catalysts were used in one pot without interfering with each other. A reaction sequence consisting of a Heck reaction and a hydroformylation was investigated (Scheme 2). First, ethylene was reacted with iodobenzene. Then, the resulting styrene was converted with CO/H_2. Besides the individual immobilized catalysts, the SAPC sample containing both complexes on the support was also reacted. In both cases, the yield of the Heck products was moderate. The mixed system, however, showed a better activity. The palladium complex seemed to gain from the presence of the rhodium complex. The latter instead showed a strong deterioration in its activity and *n/i* selectivity (cf. Table 1). When the individual catalysts were applied simultaneously, the hydroformylation catalyst showed high activity but low selectivity. The *n/i* ratio was only 0.49, which does not match the selectivities obtained with other Rh-SAPC systems.



Scheme 2 Heck reaction/hydroformylation reaction sequence

Table 1 Heck-Hydroformylation reaction sequence[a]

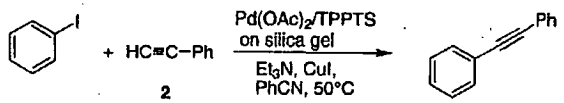
Entry	Catalyst	Heck reaction Yield (%)	Hydroformylation[b]		
			Yield (%) linear	Yield (%) branched	*n:i*
1	Pd-SAPC+Rh-SAPC	50.5	29.6	60.3	0.49
2	(Pd+Rh)-SAPC[c]	68.6	6.4	17.8	0.36

[a] For reaction conditions see Scheme 2.
[b] Yields are based on the amount of the Heck product formed.
[c] The catalyst was prepared from an ethylene glycol solution containing both Pd-TPPTS and Rh-TPPTS.

2.1.1.2 Sonogashira Reaction

The SAPC strategy was also applied to the Sonogashira reaction [19]. Therefore, $Pd(OAc)_2$ and TPPTS were immobilized on silica in a thin film of water. Two different ligand-to-metal ratios were investigated. On the one hand, five equivalents of phosphine are known to result in complete reduction of Pd(II) to Pd(0). On the other hand, two equivalents are usually recommended in the literature for standard Sonogashira couplings [20–22]. Both ratios were examined using the coupling of iodobenzene with phenylacetylene 2 in benzonitrile (Scheme 3). In recycling experiments, the system in which five equivalents of phosphine were employed showed constant activity over three runs, which then significantly dropped. With two equivalents of phosphine, only during the first run activity was retained. However, in both cases palladium leaching turned out to be high. After filtration of the solid phase the supernatant solutions were catalytically active towards newly added substrates.

Also for the Sonogashira couplings, catalytic system 1 was used as ligand. The reactions proceeded well, with yields from 58–87%. The leaching of palladium did not exceed 0.2%.



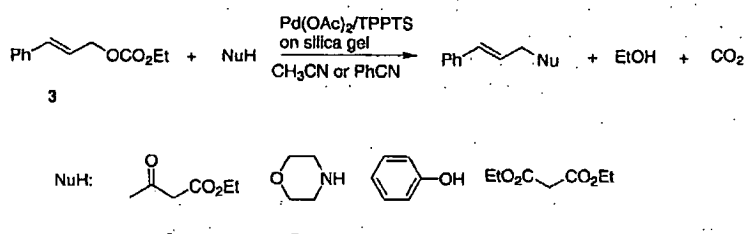
Scheme 3 Sonogashira reaction

2.1.1.3 Allylic Substitution Reaction

A different palladium-catalyzed reaction is allylic substitution. In this case, (*E*)-cinnamyl ethyl carbonate (3) and either ethyl acetoacetate (4) or morpholine (5) as nucleophiles were used as starting materials (Scheme 4) [23]. High activity was obtained when the catalyst was formed at 50 °C in solution. Under these conditions, complete reduction of Pd(II) to Pd(0) took place as judged by ^{31}P-NMR experiments. Comparing acetonitrile and benzonitrile as organic solvents, it was observed that the latter enhanced the activity of the SAPC due to its lower miscibility with water. Unlike acetonitrile, the reaction of 3 with 4 in benzonitrile proved to be superior to the analogous reaction in a homogeneous aqueous–biphasic process. In addition, it was observed that the more water-soluble substrate 5 gave improved yields under SAPC conditions.

Under optimized reaction conditions, the SAPC system showed higher activity, selectivity and stability of the catalyst compared to the homogeneous water/nitrile solvent system. Indeed, even phenol and dimethyl malonate, which were not converted under biphasic conditions, were successfully applied as nucleophiles [24].

Recycling experiments were performed to find the optimum conditions for a continuous flow process. Initially, the reactions were carried out in anhydrous benzonitrile. The reaction was terminated by filtration of the loaded support, which was then washed with benzonitrile and reused with a new batch of substrates. This procedure led to a dramatic loss of activity, for which the loss of palladium was not responsible but rather leaching of water into the organic phase. Thus, the mobility of the immobilized catalyst was reduced combined with a decrease of the activity. The use of benzonitrile/water (v/v=1/1) resulted in a constant level of activity. For a continuous flow experiment, a dry SAPC sample was prepared from $Pd(OAc)_2$ and five equivalents of TPPTS. The dry support was then placed into a reactor. The required amount of water was transferred from water-saturated benzonitrile. The test reaction was the transformation of cinnamyl ethyl carbonate with morpholine. The process achieved a TON of 2,200 and worked continuously for approx. 12 h without loss of activity.



Scheme 4 Allylic nucleophilic substitution

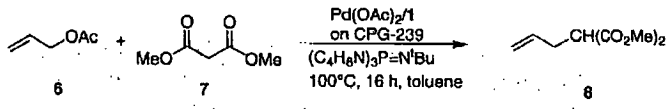
Alternatively, $Pd(OAc)_2$/TPPTS was immobilized on cellulose powder [25]. The new support was also tested in allylic substitution using 3 and 4 as starting materials (cf. Scheme 4). Cellulose-supported complexes were also dependent in their activity on the degree of hydration. Here, two maxima were observed. This was explained by the swelling properties of cellulose in water: the surface area increases by two orders of magnitude, thereby enhancing the surface accessibility and activity [26]. With 26 wt% water, the first maximum was reached. The second one was obtained when the amount of water was raised to 66 wt%. The increase of surface accessibility mentioned above was observed. Complete conversion occurred within 100 min with 66 wt%. With 26 wt%, only 60% conversion was obtained for the same reaction time.

The guanidinium phosphine 1 (cf. Fig. 2) was also successfully tested for allylic substitutions. The reaction of allyl acetate 6 and malonate 7 afforded coupling product 8 in 56% yield. The palladium leaching was determined to be about 0.3% (Scheme 5).

2.1.2 Hydrogenation

Although hydrogenation is a very important reaction in organic synthesis, there exist only a few examples using solid aqueous-phase catalysis. The feasibility of hydrogenations with a SAPC system using the Ru-BINAP derivative 9 (Fig. 3) was demonstrated [27]. Catalyst 9 dissolved in ethylene glycol was immobilized on CPG-240. Ethylene glycol was chosen because like water it is a highly polar, non-volatile liquid and immiscible with non-polar organic solvents. Unlike water, which initiates hydrolysis of theRu–chloride bond, thus leading to a lower enantioselectivity, it is inert towards ruthenium catalyst 9. As is depicted in Scheme 6, the reduction of alkene 10 to naproxen proceeded at 24 °C with a 96% enantiomeric excess for both 9 immobilized on CPG-240 and homogeneous 9 inmethanol. Ruthenium leaching was below the detection limit of 32 ppb.

It was shown that catalyst 9, dissolved in ethylene glycol, had negligible activity in the absence of CPG-240. When CPG-240 and the liquid phase containing the catalyst were loaded separately into the reactor along with substrate 10, self-assembly took place and complete conversion was observed. Additionally, all the Ru had been immobilized after the reaction on the support. In essence, it was shown that the activity was dependent on the interfacial area between the two liquid phases.



Scheme 5 Allylic nucleophilic substitution

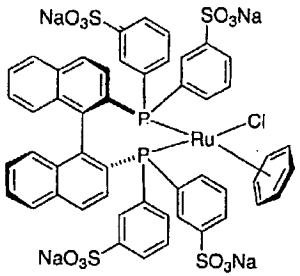


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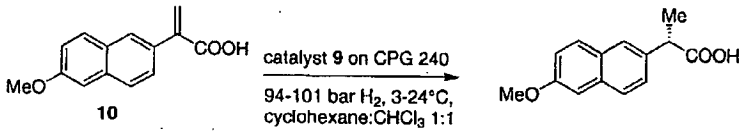
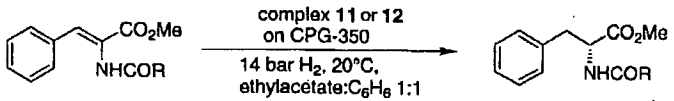
Fig. 3 Ru complex for hydrogenation



Scheme 6 Synthesis of naproxen

The catalysts 11 and 12 (Fig. 4) were used for the synthesis of phenylalanine derivatives (Scheme 7) [28]. Besides the SAPC system, both the homogeneous hydrogenation and the aqueous–biphasic system were investigated. The supported complex 11, like the homogeneous analogue, showed poor performance as far asenantio selectivities are concerned. In contrast, the aqueous–biphasic catalyst performed at least moderately enantioselective. In this context enhanced selectivity was achieved with immobilized catalyst 12. The increased ee values (from 16 to 55%) were obtained at the expense of an extended reaction time, which increased from 2 to 40 h.

A simultaneous hydrogenation of an aldehyde and an olefin was examined. The substrates for the hydrogenation protocol were 3-phenylpropionaldehyde 13 and *trans*-stilbene 14 (Scheme 8). A Ru-SAPC was used for theselective reduction of the aldehyde and additionally a Pd-SAPC for the olefin. The individual immobilized catalysts alone performed almost as well as their homogeneous counterparts as far as yields and selectivities for the functional



Scheme 7 Synthesis of protected phenylalanine

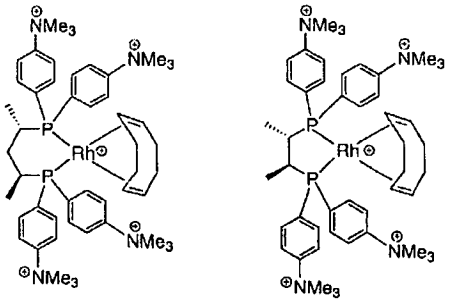
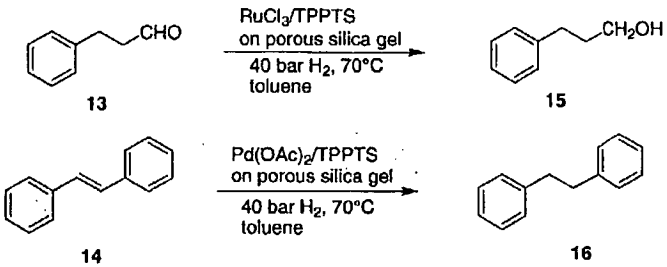


Fig. 4 Rh complexes for hydrogenation



Scheme 8 Simultaneous hydrogenation of an aldehyde and an olefin

groups are concerned. When both catalysts were supported simultaneously on silica gel, the result was the same when using both Ru-triphenylphosphine (TPP) and Pd-TPP in solution in one pot. The activity of the palladium was strongly suppressed while the yield of the alcohol15 decreased only marginally. However, using the individual SAPC samples in one pot, both reductions worked well. The yield of 15 corresponded to that of the single reaction. The 64% yield of 1,2-diphenylethane 16 was not comparable to that of the single reaction (cf. Table 2). After the reaction, the catalysts were easily separated by filtration and were successfully recycled. In addition, no metal leaching was observed.

2.1.3 Hydroformylation

Hydroformylation is a very important industrial process. Olefins are converted to aldehydes, which can be further transformed into acids, alcohols or amines. The Ruhrchemie/Rhône-Poulenc hydroformylation process is an aqueous–organic biphasic process which uses an easily separable water-soluble rhodium

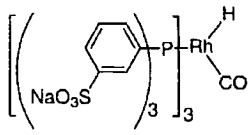
Table 2 Simultaneous hydrogenation of a mixture of 3-phenylpropionaldehyde and *trans*-stilbene[a]

Entry	Catalyst	Yield (%)	
		15	16
Homogeneous			
1	Ru-TPP	94.1	1.0
2	Pd-TPP	0.3	98.9
3	Ru-TPP+Pd-TPP	90.1	7.8
SAPC			
4	Ru-SAPC[b]	89.8	2.2
5	Pd-SAPC[b]	1.7	88.0
6	(Ru+Pd)-SAPC[c]	92.5	2.8
7	Ru-SAPC+Pd-SAPC	87.2	64.0
8	Ru-SAPC+Pd-SAPC[d]	84.4	76.6

[a] For reaction conditions refer to Scheme 8.
[b] Besides the SAPC sample, 0.5 g of silica containing 0.3 ml of water was added before the reaction was started.
[c] The catalyst was prepared from an aqueous solution containing both Ru-TPPTS and Pd-TPPTS.
[d] The catalysts for entry 7 were recycled.

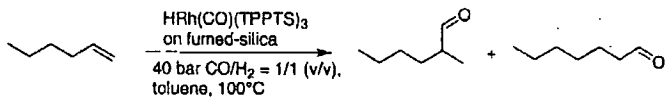
complex [29]. However, this process is only useful for the smaller olefins because only they possess sufficient solubility in water. Higher olefins have to be hydroformylated in a homogeneous process, and the catalyst is separated subsequently by distillation, which may lead to its partial decomposition. In this case, SAPC offers a promising alternative. It was shown that by using SAPC no discrimination between water-soluble and water-insoluble olefins occurred [3].

Catalyst 17 was immobilized on non-porous fumed-silica nanoparticles as support for SAPC hydroformylation (Fig. 5) [30]. In aqueous solutions, the fumed silica possesses great adsorption capacity and the active sites on its surface form strong hydrogen bonds with water molecules [31]. This makes fumed silica an ideal support for solid aqueous-phase catalysis. Additionally, a porous granular silica was also used. The hydroformylation of 1-hexene was investigated and the results were compared with those of the aqueous–biphasic hydroformylation. In all cases, *n*-heptanal was produced with a selectivity of close to 100%. The activity of the fumed-silica SAPC was comparable to that of the biphasic catalytic system with cetyltrimethylammonium bromide as additive. But the loss of rhodium was one order of magnitude lower in the case of the fumed silica than that of the latter system. The lowest rhodium leaching was observed with the system using porous silica as support. Six different kinds of commercially available fumed silicas with different surface areas and particle sizes were compared concerning their catalytic performance in the hydro-



17

Fig. 5 Complex for hydroformylation



Scheme 9 Hydroformylation of 1-hexene

formylation of 1-hexene (Scheme 9). The prevailing trend was that the reaction rate and the selectivity towards the linear aldehyde increased with smaller particle size and higher surface area of the support.

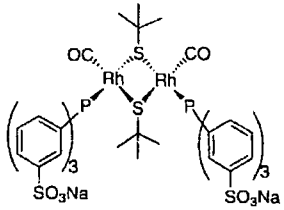
The water content of the support exhibited an interesting influence on the activity. With porous silica as support, the dependence of the activity on the water content showed a single maximum. On the other hand, fumed silica showed high activity over a wide range of hydration states. The highest conversions took place between 40 and 64 wt% water, almost independently of the ligand/rhodium ratio and the type of fumed silica used. The regioselectivity of the hydroformylation was not influenced significantly by varying the amount of water. With a molar olefin/rhodium ratio of 2,500, the highest reaction rates were obtained.

The influence of the triphenylphosphine trisulphonate trisodium salt (TPPTS)/metal ratio was low and conversion as well as the degree of regioselectivity remained almost constant. However, the reaction performance was dependent on the pressure applied. Lower pressure resulted in increased regioselectivity in favour of the linear aldehyde, but also in decreased reaction rate. The authors reasoned that coordination of the phosphine ligand to the metal was preferred over coordination by CO because of the lower CO concentration. Additionally, ^{31}P-NMR spectroscopy was carried out to examine the phosphine species on the support. After the preparation of the supported catalyst, three different signals were observed: free TPPTS, coordinated TPPTS and oxidized TPPTS (OTPPTS). The amount of OTPPTS increased during the reaction. Pretreatment of the silica with basic inorganic salts like Na_2CO_3 or Na_2HPO_4 suppressed the oxidation, which was in accordance with previous results [32]. In these studies, complex 17 was immobilized on a commercially available silica. In order to obtain a mobile complex, 40% D_2O was added. The first observation was that the amount of oxidized TPPTS of the SAPC sample was three times higher than in the case of complex 17 dissolved in D_2O. Due to the immobi-

lization, it also seemed that a new rhodium-TPPTS species was formed. This was indicated by a reduced rhodium-to-ligand ratio (changing from 1:3 to 1:2) and different peaks in the ^{31}P spectrum. This new species interacted strongly with the support as it was impossible to remove it by simple washing with D_2O. The new complex was assigned to be $[Rh(CO)(TPPTS)_2]_n$ (n=1,2). When the catalyst loading on the support was increased, the signals for the original complex **17** appeared. It was assumed that **17** reacted with the silica forming the new species, which then coated the surface of the support. When the whole surface was covered with the new complex, excess of **17** remained unchanged. It was assumed that the acidic property of the silica facilitated the oxidation of the basic TPPTS and therefore alteredcomplex **17**. Pretreatment of SiO_2 with Na_2CO_3 or TPPTS led to a reduced acidic environment on the support, so that no structural change occurred at all and **17** remained intact.

In a multifunctional process, a Rh/TPPTS system was applied besides a Pd/TPPTS system for a tandem Heck reaction/hydroformylation sequence in one pot (cf. Scheme 2). The results are described in more detail in Sect. 2.1.1.1.

A different complex **18** [33] was immobilized on silica for the hydroformylation of 1-octene (Fig. 6) [34]. The catalyst preparation was done using the self-assembly method. In an earlier paper, it had been demonstrated that catalyst **18** requires an excess of phosphine in order to suppress the formation of an inactive tetracarbonyl complex under CO pressure [35]. Hence, the SAPC system was first examined concerning the optimal phosphine-to-rhodium ratio. With a ratio of 6, the highest conversion was observed with about 80% in favour of the linear aldehyde. Addition of more phosphine caused two effects: (a) the selectivity for the linear product increased and (b) the degree of conversiondecreased. The reason for this result was seen in the enhanced competition between the ligand and the olefin for the coordination to the metal centre. But while the effect on the selectivity was low, the conversion dropped by about 20%. The major part of the study dealt with the influence of the hydration of the support on the catalytic performance. It was shown that the conversion increased considerably with total saturation of the silica pores, which corresponded to 16.5 wt%. Excess of water resulted in enough mobility of the catalyst on the surface. Hence, between 19 and 44 wt% the highest degree ofconversion was observed, the maximum being at 24 wt%. Above 44 wt%, the activity decreased again because the water, and subsequently the catalyst, was not sufficiently retained on the silica. In the range 19–44 wt%, n/i ratios from 3:1 to 8:1 were obtained. At this point the role of the pores inside the support was not clear. Thus, the influence of porous and non-porous supports was investigated. When non-porous glass beads were used, no catalytic activity was observed, only rhodium leaching into the organic phase took place. Having two silicas with different pore sizes, the dependence on the conversion couldbe demonstrated. Supports with large pores behaved according to the proposed mechanism [3]. The reaction took place inside the pores. Therefore, the maximum degree of conversion was seen before the total filling of the pores. When the pores were completely filled, the activity decreased, because the organic solvent could not penetrate the pores and the contact between catalyst and substrate was diminished. The silica with smaller pores behaved differently. The pores served as a storage for TPPTS and the catalyst. The reaction occurredat the external surface of the support. Therefore, complete saturation of the pores was necessary for high conversion.



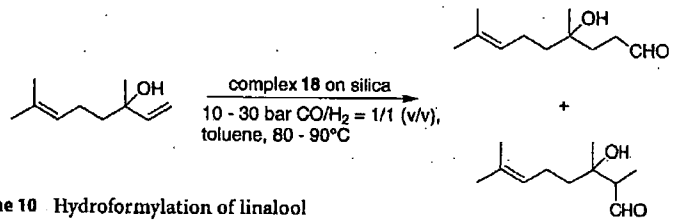
18

Fig. 6 Complex for hydroformylation

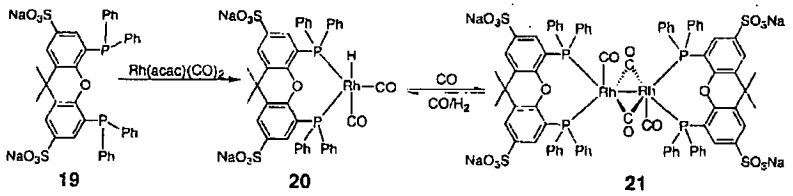
Catalyst **18** was then used to investigate the kinetics of the hydroformylation of linalool in toluene (Scheme 10) [36]. The reaction proceeded well with the aldehydes being the sole products. The selectivity in favour of the linear aldehyde was in the region of 70%.

The turnover frequencies measured at different temperatures were comparable to those found for hydroformylations using other strategies [1, 3, 33, 35]. To develop the kinetic model, the effects of the linalool and the catalyst concentration and of the total carbon monoxide and hydrogen pressure on the outcome of the hydroformylation were investigated. In all cases, the reaction rate was enhanced by a first-order dependence. The results were in good agreement with the calculated model. The activation energy was found to be 14.5 kcal mol^{-1}.

The metal precursor $Rh(acac)(CO)_2$ and **19** were loaded onto CPG-240 with a ligand-to-Rh ratio of 10:1 (Scheme 11) [37]. The in situ formed complex **20** was studied in hydroformylation experiments using 1-octene and compared with $Rh(TPPTS)_3$ on silica. Catalyst **20** was very selective in favour of linear aldehydes (n/i=40:1). Even after ten runs, the selectivity remainedhigh. With TPPTS as ligand, only a regioselectivity of n/i 3:1 was achieved. But the activity of complex **20** in toluene was poor (1 h^{-1}). It could be enhanced by about 15 times when neat 1-octene instead of toluene was applied (15 h^{-1}). Increasing the



Scheme 10 Hydroformylation of linalool



Scheme 11 Complex 20 and the reversible switch into its storage form

temperature from 80 to 100 °C further enhanced the activity (55 h^{-1}). A concentration effect concerning 1-octene was not observed in the case of catalyst 17. But here an increased activity with rising temperature also occurred by the same factor. Complex 20 could not match the activity of 17 but had the advantage of higher regioselectivity and, furthermore, the reusability proved to be better. All runs showed no loss in activity, and no traces of metal were detected in the product phase (detection limit 1 ppm). Instead, the TPPTS system showed good performance only over three runs. In the fourth run, the activity decreased, the regioselectivity dropped and 50% of 1-octene was isomerized and not converted into aldehyde. Additionally, complex 20 could be stored for weeks by transforming it into the more stable dimeric complex 21 (Scheme 11). This was achieved by changing the atmosphere from a mixture of CO/H_2 to pure CO. Importantly, this process was reversible and the catalyst could afterwards be reused without loss of activity.

2.2 Supported Ionic Liquid Catalysis

Ionic liquids have attracted significant attention as alternative reaction media for catalysis in biphasic systems [38–42]. Because of their highly polar nature they are immiscible with many organic solvents. This forms the basis for biphasic reactions where the catalyst is present in the ionic liquid while the substrate stays in the organic phase.

A combination of the advantages of ionic liquids and heterogeneously supported materials was achieved by covering silica gel particles with a thin film of an ionic liquid [43]. This reduces the required amount of ionic media, which is beneficial from an economic and toxicological point of view. Both hydroformylation and hydrogenation reactions were investigated [43, 44].

2.2.1 Hydroformylation Reactions with an Ionic Liquid-Supported Catalyst

In the case of hydroformylation reactions, thesilica gel was modified with a monolayer of covalently attached ionic groups as depicted in Fig. 7, covering approximately 35% of the silica gel's hydroxyl groups. Treatment of this

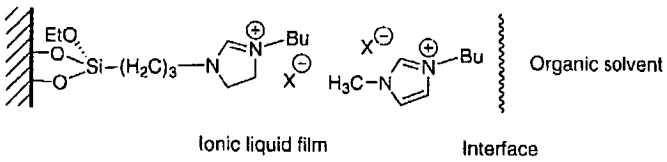


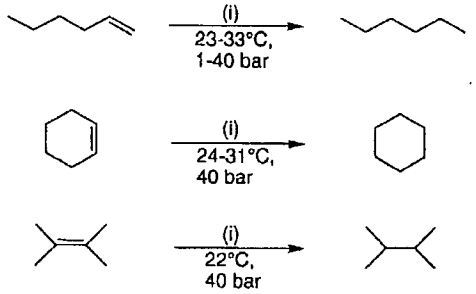
Fig. 7 Layer of ionic liquid supported on a modified silica gel

monolayer surface with a mixture of the rhodium catalyst precursor and ligands (TPPTS, TPPTI, ratio Rh:P 1:10) dissolved in acetonitrile and ionic liquid phase ([bmim][BF_4] or [bmim][PF_6], 25 wt% loading) followed by removal of thesolvent under reduced pressure yielded the immobilized multilayered supported catalyst as a free-flowing powder. The supported catalyst was tested in the hydroformylation of 1-hexene, where it performed reasonably well. The observed TOFs (TOF = turnover frequency) ranged from 56 to 65 min^{-1} (with different ligand-solvent combinations, yields from 33 to 46%), which is significantly higher than the observed TOFs with the biphasic non-supported systems (2.4 to 23 min^{-1}, yields from 11 to 70%). The enhanced activity was attributed to the general increase of interface area and the higher local concentration of catalyst at the interface. Compared to the homogeneous system, where a TOF of 400 min^{-1} (yield 95%) was observed, however, the activity was significantly lower. Nevertheless, the supported ionic liquid system is attractive due to its convenient product separation. Metal leaching ranged from 0.07 to 2.1%, which lies in the range of biphasic reactions. The clear advantage over the biphasic reactions is the decreased loss of expensive ionic liquid phase.

2.2.2 Hydrogenation Reactions with an Ionic Liquid Supported Catalyst

[Rh(NBD)(PPh_3)$_2$]PF_6 (NBD=norbornadiene) as a pre-catalyst was immobilized by treatment with acetone, [bmim][PF_6] and silica gel (untreated, without attached ionic liquid fragments). The obtained material was a free-flowing powder despite an ionic liquid loading of 25 wt%. The estimated thickness of the ionic liquid layer was 6 Å.

The supported catalyst was successfully employed using different substrates, depicted in Scheme 12. For the reduction of 1-hexene a TOF of 447 min^{-1} (99% yield, 30 °C, 600 psi) was observed for the supported catalyst, compared to 46 min^{-1} (29% yield, 50 °C, 600 psi) for the homogeneous system. This enhanced activity is supposedly due to the absence of a coordinating solvent that blocks coordination sites on the Rh, thus inhibiting the reaction significantly. Comparison with the biphasic reaction showed a TOF of 4 min^{-1} under similar conditions. This can be explained by the higher local concentration of catalyst in the case of the supported system. The catalyst activities for the hydro-



Scheme 12 Hydrogenation of olefins: (i) H_2, Rh catalyst in supported ionic liquid

genation of cyclohexene and 2,3-dimethylbutene were slightly reduced, due to the decreased accessibility of the double bond in these substrates.

Catalyst leaching was not observed and the same catalyst was used for 18 batch runs without significant loss of activity. Both hydroformylations and hydrogenations clearly showed that supported ionic liquid catalysis is a very useful and efficient principle.

3
Immobilization by Polar Interactions

3.1
Catalysts Bound by Hydrogen Bonding

3.1.1
Hydrogenation with Hydrogen Bonded Catalysts

In this and the following sections we describe the methods which do not need a hydrophilic solvent to retain the catalyst on the surface of the solid support. Utilization of hydrogen bonding for the non-covalent immobilization of Ru and Rh complexes on silica gel was investigated in detail [45–47]. The loading of the support was done without further covalent modification of the silica gel, and there was no need for a solvent film covering the support particles.

The investigated supported complexes **22** and **23**, outlined in Fig. 8, were used for hydrogenations of alkenes, nitriles and α,β-unsaturated ketones. Furthermore, **23** was used in the reduction of different heterocycles like benzothiophene, quinoline, indole, dibenzothiophene and acridine. The supported chiral Rh complexes, depicted in Fig. 9, were used for hydrogenation reactions with prochiral olefins.

The immobilization procedure consisted of dissolving the complexes in anhydrous dichloromethane and subsequent stirring with activated silica gel (ac-

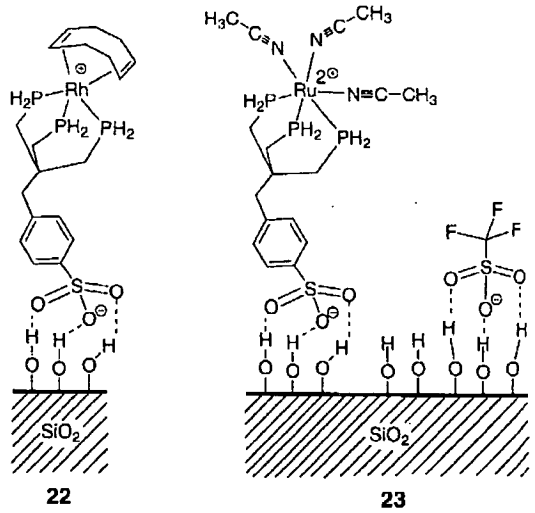


Fig. 8 Catalysts immobilized by hydrogen bonding on silica gel

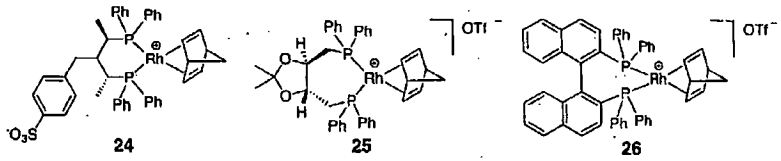
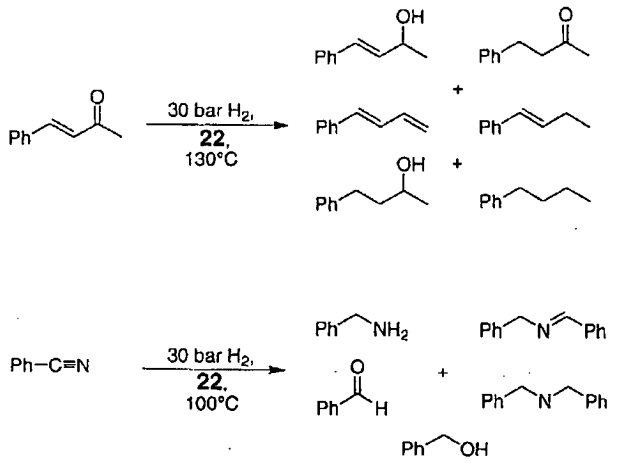


Fig. 9 Chiral Rh complexes

tivated by heating to 300 °C for several hours to remove physisorbed water). The progress of silica loading could be observed as the yellow colour of the solution faded and the silica gel turned increasingly yellow. After filtration the supported catalysts were obtained, with 2 wt% catalyst loading in the case of the non-chiral and 1 wt% in the case of the chiral complexes **24**, **25** and **26**.

The supported catalyst **22** was tested in the reduction of benzylideneacetone and benzonitrile (Scheme 13). Thus, the supported catalyst, the substrate and solvent*n*-octane were combined in the reaction vessel followed by charging with hydrogen (30 bar) and stirring at 130 °C. The reaction product was removed by filtration and the filtrate was analysed by GC.

In the case of benzylideneacetone, the conversion of 61% was significantly lower than with a biphasic aqueous–organic catalyst system (87% conversion) or the conventional homogeneous catalyst system (100% conversion). However, the observed selectivity in the case of catalyst **22** was 96%, i.e. almost selective reduction of the olefinic moiety took place whereas the carbonyl substructure

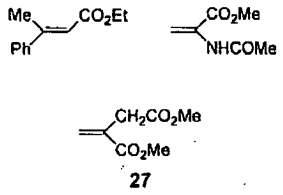


Scheme 13 Hydrogenation of an unsaturated ketone and a nitrile

remained nearlyuntouched. This is not observed when the biphasic (87% of the desired product) or the homogeneous catalyst (1% of the desired product) is used. In the case of the homogeneous catalyst both olefinic and carbonyl substructures were reduced.

With benzonitrile as substrate, catalyst 22 performed significantly better than the biphasic catalytic system. Both conversion (95%) and selectivity (92%) of the supported system were superior compared with the performance of the biphasic system (25% conversion, 65% selectivity), where the main product was not even the desired product. The best performance, however, was achieved with the homogeneouscatalyst, which reached 98% conversion and 100% selectivity. Nevertheless, the easy separation and reusability of the catalyst make the system 22 attractive for use in hydrogenation reactions.

As mentioned above, catalyst 23 was successfully applied to the hydrogenation of various heterocycles, where only the heterocycle was hydrogenated, whereas annulated aromatic systems remained untouched [48]. The reduction of prochiral olefins (Fig. 10) with the supported chiral catalysts gave generally



27

Fig. 10 Prochiral olefins

nearly quantitative yields, but the enantioselectivity was mediocre, 53% in the best case using catalyst 24 and olefin 27.

In the same manner mentioned above, [(*R*,*R*)-Me-(DuPHOS)Rh(COD)]OTf [Me-DuPHOS=1,2-bis(2,5-dimethylphosphacyclopentyl)ethane] 28 (Fig. 11) was immobilized via hydrogen bonding of the triflate [49]. The immobilized complex was found to exhibit high catalytic activity and selectivity for the hydrogenation of three prochiral α-enamide esters (Fig. 12). For example, hydrogenation of 29 in hexane at room temperature led to complete conversion (99%) with high enantioselectivity (99%). Reduction of the other two olefins 30 and 31 gave similar results. Those reactions were superior to homogeneous reactions in hexane, where comparable conversion could be observed but with significantly reduced enantioselectivity (from 85 to 87%). Only the homogeneous reduction in MeOH, which generated similar conversion and enantioselectivity, could rival the reaction utilizing the supported system in hexane. According to the authors, leaching of catalyst could not be observed and repeated application without loss of conversion orselectivity proved the reusability of the supported catalyst.

Another more recent publication reported the grafting of chiral Rh complexes on silica gel via hydrogen bonding [50]. Different chiral ligands (Fig. 13) were converted to Rh trifluoromethanesulphonate complexes and immobilized applying the same immobilization technique mentioned above, the anionic part tethered non-covalently to the surface of the silica particles. Those complexes were applied in the hydrogenation of (*E*)-α-phenylcinnamicacid to 2,3-diphenyl propanoic acid, carried out at 20 barH_2 and 40 °C. Conversion (up to 90%) and enantioselectivity (up to 97%) were generally higher than with the same ligands in homogeneous complexes (conversion up to 88%, ee up to 83%).

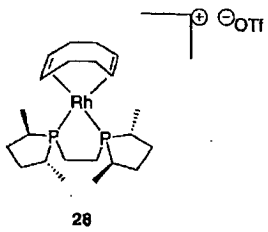


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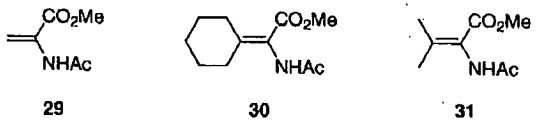
Fig. 11 Chiral hydrogenation catalyst



29 30 31

Fig. 12 More prochiral olefins

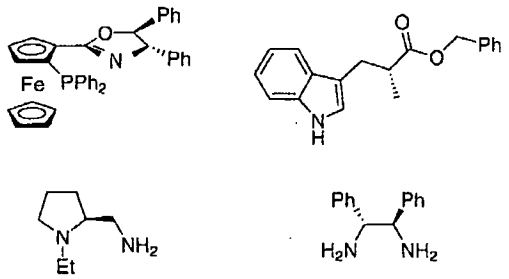


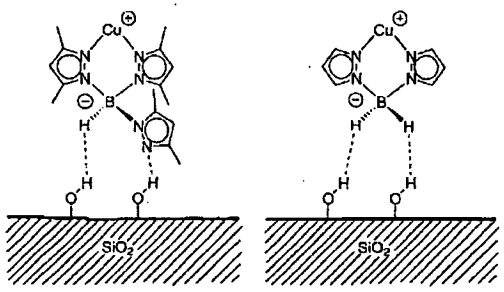
Fig. 13 Different chiral ligands

3.1.2
Epoxidation with a Supported Hydrogen-Bonded Catalyst

Besides hydrogenations, epoxidations with hydrogen-bonded catalysts were reported [51, 52]. Copper(I) pyrazolborates (Fig. 14) were immobilized on silicagel by dissolving the complexes in dichloro methane and subsequent stirring forseveral hours and filtration.

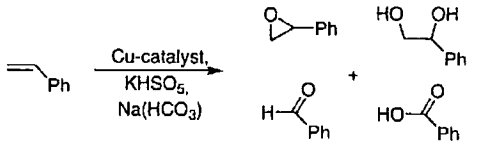
The air-labile complexes were supposed to interact with the support not only through classical hydrogen bonds but also through so-called non-classical hydrogen bonds. These non-classical hydrogen bonds, also called dihydrogen bonds, are similar to those recently found in BH_3NH_3 [53]. As proposed by Crabtree, these bonds must be interpreted as the interaction of the NH proton, or in this case, as the OH proton and the BH bond as a whole.

Epoxidation reactions with the immobilized catalysts 32 and 33 (Scheme 14) using oxoneas oxidant did not work as well as the homogeneous reactions, however. Whereas the homogeneous reaction provided styrene oxide in 60% (with catalyst 33) and 70% (with catalyst 32) yield (corresponding to the oxidant) with only a small amount of benzaldehyde by-product (<5%), the heterogeneous reaction provided mainly amixture of by-products and styrene. The

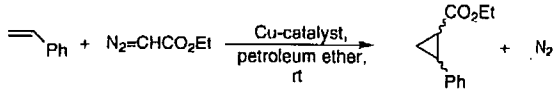


32 33

Fig. 14 Copper complexes bound to silica gel



Scheme 14 Epoxidation with oxone and a supported Cu catalyst



Scheme 15 Cyclopropanation with a supported Cu catalyst

main by-product, 1-phenylethanediol, generated by nucleophilic ring opening, is a consequence of the acidic nature of the solid support. If all by-products are taken into consideration, an overall yield of 57% (for 32) and 68% (for 33) was achieved, which is lower than under homogeneous oxidation conditions.

3.1.3
Cyclopropanations with a Supported Hydrogen-Bonded Catalyst

Apart from epoxidations, cyclopropanations were performed with the same immobilized catalysts mentioned above [54]. However, the performance of the catalytic system for cyclopropanations was significantly better than for epoxidations.

Cyclopropanation reactions were carried out with ethyl diazoacetate as carbene source and styrene, using petroleum ether as solvent (Scheme 15). After completion of the reaction, the mixture was filtered in order to separate catalyst and products. The heterogeneous system provided slightly higher yields (up to 90%) and similar lower diastereoselectivities compared to the homogeneous system.

To summarize the reactions above, the feasibility of immobilization via hydrogen bonding has been demonstrated, and the generally low leaching of catalyst, the relatively simple catalyst preparation and thehigh activity, and in some cases high selectivity, make this approach veryattractive. However, the choice of solvent is very important to avoid highercatalyst leaching. For example, most of the catalysts mentioned above arewashed off the solid support with alcohols like MeOH or EtOH, whereas thehydrogen bonding remains intact with dichloromethane.

3.2
Heck Reactions with Catalysts Immobilized by Ionic Interactions

Recently, the heterogenization of a water-soluble complex via an ion-exchange process was described [55]. As solid support, a layered double hydroxide (LDH)

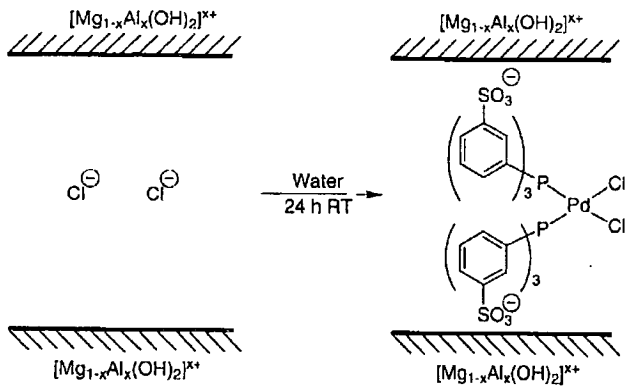


Fig. 15 Pd complex immobilized between thelayers of a double hydroxide by an ion exchange process

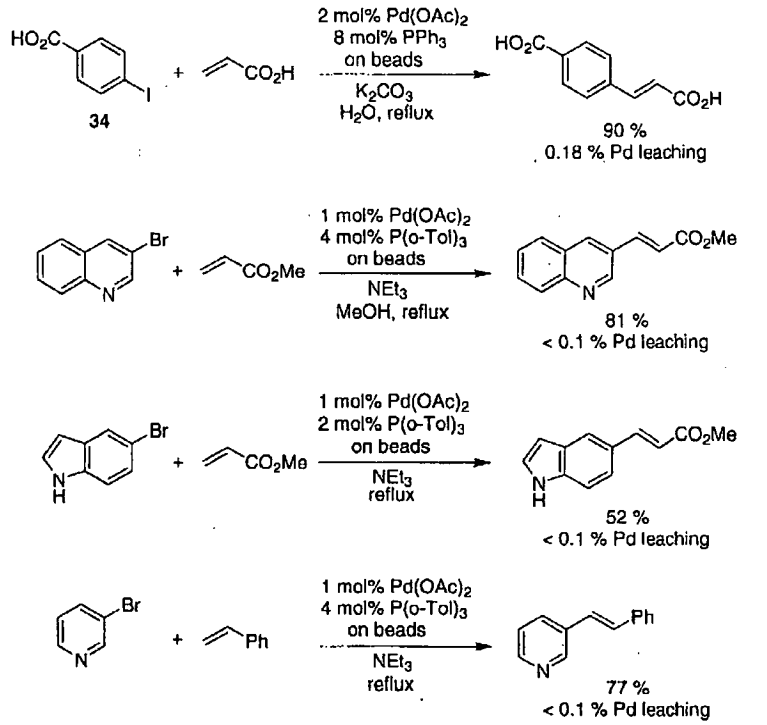
consisting of alternating cationic $[Mg_{1-x}Al_x(OH)_2]^{x+}$ and anionic $Cl^- \cdot nH_2O$ layers was employed. The complex $Pd(TPPTS)_2Cl_2$ was immobilized by stirring for 24 h in decarbonized water with the suspended solid support [56]. After filtration the resulting solid was washed and dried (Fig. 15).

The supported catalyst obtained was investigated in Heck arylation reactions, where the olefin, haloarene, supported catalyst, tributylamine and DMF were stirred at 120 °C under nitrogen. The supported catalyst performed very well, with excellent yields and high trans-selectivity. For example, the reaction of *p*-bromoanisole with styrene afforded the coupled product in 87% yield. This result is good, considering the use of a donor-substituted bromoarene, which generally do not perform well in Heck reactions. The observed leaching of total Pd was below 0.5%. The yields observed using this technique were generally higher than those using the homogeneous catalyst. This is supposedly due to some beneficial interactions of the LDH support during the catalytic cycle. The higher activity, low Pd leaching, reusability and easy catalyst separation make this immobilization process attractive.

4
Immobilization by Hydrophobic Interactions

4.1
C–C Couplings with Catalysts Immobilized on Reversed-Phase Solid Support

The use of hydrophobic interactions for the non-covalent immobilization of catalysts is another possible concept for attachment of catalysts. The concept is based on hydrophobic interactions between commercially available reversed-phase silica gel and a hydrophobic anchor attached to catalysts.



Scheme 16 Heck reactions with catalyst on reversed-phase silica gel

Utilizing this principle, Heck reactions were performed [57]. The silica gel was derivatized with a C_8H_{17}-trimethoxysilane to obtain the desired reversed phase properties, followed by treatment with palladium acetate and triphenylphosphine in cyclohexane. After removal of the solvent, an air-stable catalyst supported on reversed-phase silica gel (RPSG) was formed. This supported catalyst was employed with variable success in Heck C–C coupling reactions, as depicted in Scheme 16.

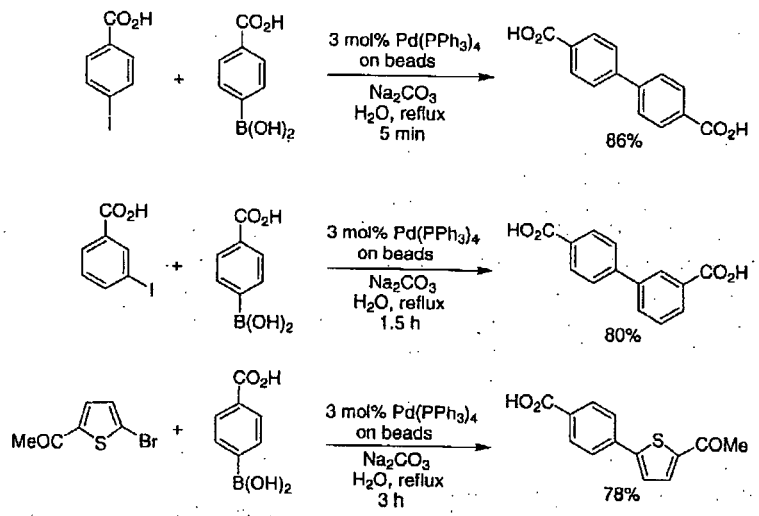
The leaching of total Pd was very low, ranging from 0.02 to 0.18%. For example, *p*-iodobenzoic acid (**34**), acrylic acid, supported catalyst (2 mol% Pd) and K_2CO_3 were dissolved in water and heated under reflux for 2 h. After filtration the coupled product could be isolated in 90% yield. The reactions were performed with different solvents, not only water, but also methanol, Et_3N and DMSO. Hence, there was no requirement to use water-soluble substrates. Another advantage of this reversed-phase silica gel method is that more polar substrates compared to the conventional homogeneous Heck reaction can be employed. In homogeneous Heck reactions polar substrates are difficult to

separate from metal contamination. Examples of polar substrates are the *N*-containing heterocycles (quinoline, indole and pyridine) shown in Scheme 16.

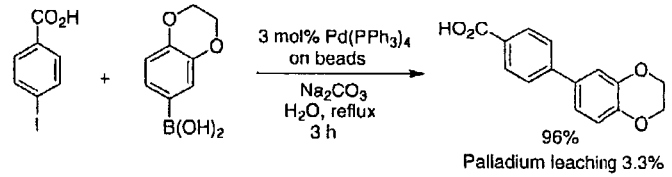
Later, the principle of hydrophobic catalyst immobilization was extended to Suzuki reactions [58]. Instead of P(*o*-Tol)$_3$ as a phosphine ligand, PPh$_3$ was used. Grafting of the catalyst onto RPSG followed the same procedure mentioned above. Several haloarenes were reacted with *p*-carboxyphenyl boronic acid in water under reflux (Scheme 17). The yields obtained were similar to those reached with homogeneous catalysts. Observed leaching was low, reaching from 0.06 to 0.63% of total palladium. If *p*-chlorobenzoic acid was used as a reactant, no coupling was observed. However, immobilization of other non-polar ligands should be possible. The presence of the glass beads seemed to have a beneficial influence on the rate of reaction. Thus, the reaction of *p*-iodobenzoic acid proceeded to completion within 5 min, while conventional Pd(PPh$_3$)$_4$ gave only 50% conversion after 7.5 h. This increased reaction rate was attributed to the large contact area between water and supported catalyst. The catalyst was recycled once and reused without any loss of activity.

Both Heck and Suzuki reactions proved the worth of hydrophobic immobilization, and in the latter case the higher reaction rate was an additional advantage. Beneficial, too, is the fact that conventional catalysts could be used without further modification, because there was no need to adjust the ligand solubility. A major drawback of this procedure, however, is the restriction in the choice of suitable reactants.

Since non-polar reactants are able to wash down the equally non-polar catalyst, the range of suitable reactants is limited to more or less polar substances.



Scheme 17 Suzuki reactions with catalyst on reversed-phase silica gel



Scheme 18 Suzuki reaction with less polar boronic acid

Scheme 18 depicts a Suzuki coupling with a non-polar boronic acid and catalyst leaching of 3.3% due to this reagent.

4.2 Immobilization on Fluorous Reversed-Phase Silica Gel

Ever since the initial report by Horváth and Rábai [59], fluorous biphasic systems have received much attention as a tool for the separation and recovery of reagents or catalysts. Accordingly, a number of reviews on his topic have appeared in the literature [60–65]. The concept is based on the temperature-dependent immiscibility of perfluorinated solvents and common organic solvents. Organic compounds are usually not soluble in perfluorinated solvents, but the solubility greatly increases when perfluoroalkyl chains, so-called perfluoro tags, are attached to the molecule (Fig. 16).

Accordingly, the partitioning coefficient between organic and fluorous solvents of a molecule depends on the presence of perfluoro tags. This has been employed in numerous separation strategies based on phase separation of organic and fluorous solvents [64, 65]. Perfluorinated solvents have the advantage that they are chemically inert and, thus, not flammable and of low toxicity. But besides their relatively high price, their major drawback is that they are potent greenhouse gases by virtue of their volatility, inertness, which causes long atmospheric lifetimes, and their strong IR absorption [66]. Thus, it would be highly desirable to omit perfluorinated solvents, while still making use of fluorous–fluorous interactions. In this context the thermomorphic behaviour of certain perfluoro-tagged compounds was employed [67, 68]. In a more general approach, fluorous reversed-phase silica gel (FRPSG) (35) (Fig. 17) has been utilized as a solid support for the non-covalent immobilization of perfluoro-tagged Pd catalysts [69]. As such it was applied to C–C couplings in organic solvents.

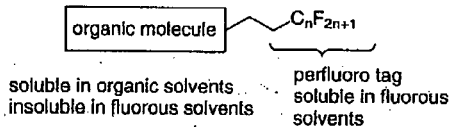


Fig. 16 Schematic representation of a perfluoro-tagged molecule

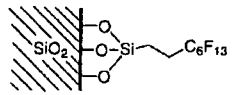


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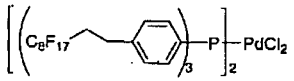
Fig. 17 Fluorous reversed-phase silica gel

For the immobilization of perfluoro-tagged bis(triphenylphosphine) Pd complexes **36, 37, 38** (Fig. 18), FRPSG **35** was shaken with a solution of the complex in a volatile solvent (e.g. diethyl ether) and the solvent was evaporated. The thus immobilized pre-catalyst is an air-stable, free-flowing powder. This, along with the dilution of the catalyst by FRPSG, facilitates the precise handling of small catalyst amounts, especially in parallel reactions. Typically, the FRPSG was loaded with 10 mg of complex per gram of FRPSG, which corresponds to 3 μmol/g. Suzuki couplings of phenylboronic acids with aryl bromides were carried out in biphasic mixtures of DME and aqueous Na_2CO_3 (Scheme 19).



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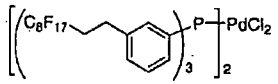

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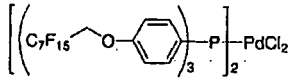

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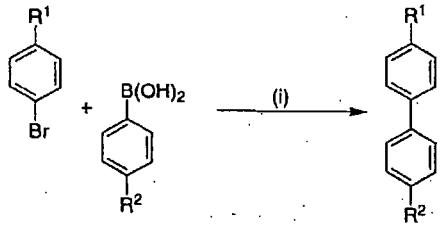
Fig. 18 Perfluoro-tagged Pd complexes

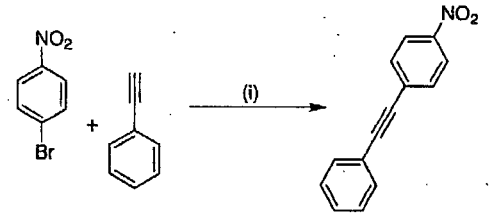


Scheme 19 Suzuki reaction with catalyst on FRPSG: (i) 0.1 mol% Pd, DME, 2 M aq. Na_2CO_3, 80 °C, 16 h

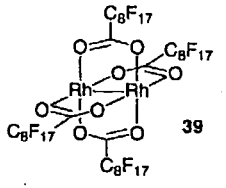
For the isolation of the product, the catalyst supported on FRPSG was filtered, washed with DME and water, and reused for further reactions. With catalyst loadings of 0.1 mol% yields were high for electron-deficient aryl bromides, and recycling of the catalyst was successful with very reactive substrates like *p*-bromonitrobenzene or *p*-bromobenzonitrile.

This catalyst immobilization on FRPSG was also employed in the Sonogashira coupling of *p*-nitrobromobenzene and phenylacetylene (Scheme 20). The same strategy was used for the immobilization of dirhodium(II) perfluorocarboxylates [70]. Rhodium complex **39** was adsorbed on FRPSG and used as catalyst for the alcoholysis of silanes (Scheme 21). In the solventless protocol, 0.1 mol% of supported catalyst was mixed with 1-octanol and triethylsilane, which led to complete conversion within 24 h. The catalyst could be recycled by simple filtration, with Rh leaching of 2.6%. Despite the small leaching, the activity was slightly reduced, which was attributed to slow catalyst decomposition.

The attempt to immobilize a perfluoro-tagged Co(III) salen complex **40** (Fig. 19) on FRPSG did not lead to active catalysts [71]. While complex **40** was active in solution as catalyst for the hydrolytic kinetic resolution of epoxides, the adsorbed complex was inactive. The authors attributed this to site-isolation on the solid support, which counteracts the proposed cooperative reaction mechanism [72, 73].



Scheme 20 Sonogashira reaction: (i) 2 mol% catalyst on FRPSG, CuI, *n*-Bu_2NH, DMF, 100 °C, 14 h



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Scheme 21 Alcoholysis of $HSiEt_3$

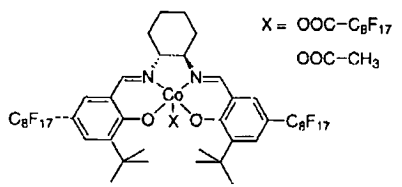

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Fig. 19 Perfluoro-tagged chiral Co-salen complex

The important feature of the immobilization on FRPSG is the selectivity of the interactions. The perfluoro-tagged catalyst exhibits a preference for the fluorous solid support in organic media as well as in aqueous media. Neither non-polar organic substances nor inorganic salts adhere appreciably to the FRPSG. This is a unique distinction between FRPSG on the one hand and reversed-phase materials or polar supports like silica gel on the other hand. Since it allows one to work with polar and non-polar liquid phases simultaneously, which is often necessary during work-up, immobilization on FRPSG will certainly see further application in the near future.

In combinatorial chemistry FRPSG can also be used as a solid support for organic synthesis. As a first example of this strategy, the synthesis of a library of 16 quinazoline-2,4-diones starting from perfluoro-tagged benzyl alcohol was described [74].

5 Conclusion

As detailed in this overview, the non-covalent attachment of catalysts on a solid support is an important additional technique for the separation and recovery of catalysts from reaction mixtures. Such non-covalent immobilization strategies bring together a number of advantages of solution-phase chemistry and solid-phase supported chemistry. The catalysts can be separated from reaction mixtures by simple filtration. The pre-catalysts can be prepared and characterized in solution. The underlying principle is partitioning between a solid phase or a supported liquid phase and a liquid reaction phase of different solvating power.

Silica gels and controlled-pore glass, which were covered with thin films of polar phases such as water, ethylene glycol or ionic liquids, were used as polar solid supports. These systems are limited to very polar, usually ionic catalysts and non-polar reaction media in order to prevent catalyst leaching. This in turn, can be limiting to the range of substrates. Existing catalytic processes in common liquid–liquid biphasic systems can be easily transferred to supported liquid-phase conditions. At the same time the interfacial area between the

phases can be increased dramatically. The support materials are inexpensive and readily available on the large scale. For supported aqueous and ethylene glycol films the liquid phase is very cheap, but a drawback is that the amount of liquid layer has to be carefully optimized for every process. For supported ionic liquids the liquid phase is very expensive, but the necessary amount is much lower as compared with the corresponding liquid–liquid biphasic system. Although it is conceivable that these strategies may find application in laboratory synthesis, the major part of research has been directed towards industrial processes.

Similarly, silica gel without a liquid film and clay-like materials have been used as polar solid phases for the attachment of catalysts by ionic interactions or hydrogen bonds. The main advantages and limitations are along the lines mentioned above for supported liquid phases.

Reversed-phase silica gel has been used to immobilize hydrophobic catalysts. This strategy is limited to polar solvents like H_2O, methanol, triethylamine or DMSO and to polar substrates and therefore it is complementary to immobilizations using polar supports.

These strategies have in common that they rely on a large difference in polarity of catalysts and substrates, where one component is very hydrophilic and the other very lipophilic. While such strategies can be successful for single reactions or smaller classes of substrates with similar solubility, it cannot be applied generally to substrates of differing polarity. An advantage is that the supports are often inexpensive and available in large quantities. Since optimization of every single reaction is necessary, these strategies are attractive mainly for industrial processes, while application on the laboratory scale will probably be limited to special cases.

Fluorous reversed-phase silica gel has been used as the support for perfluoro-tagged catalysts. The main advantage is the solvophobicity of perfluoroalkyl tags. They result in a selective partitioning onto the fluorous reversed-phase silica gel, while untagged components possess no affinity to the fluorous phase. As a consequence, polar as well as non-polar reaction media can be used, which makes this strategy applicable to a broader range of reaction and work-up conditions. It is conceivable to further adjust the reactivity by release from the support during the reaction and re-adsorption after a solvent switch. The main limitation is the necessity to modify both the solid support and the catalyst with perfluoroalkyl tags, but FRPSG and an increasing number of modified catalysts are becoming commercially available. This strategy will probably find use mainly in laboratory applications and it might also be applied to special processes of fine chemical production.

It remains to conclude that non-covalent catalyst immobilization is an interesting alternative to covalent attachment and this growing field will certainly influence catalytic processes.

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APPENDIX H

JOC Article

Synthesis, Reaction, and Recycle of Light Fluorous Grubbs–Hoveyda Catalysts for Alkene Metathesis†

Masato Matsugi and Dennis P. Curran*

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

curran@pitt.edu

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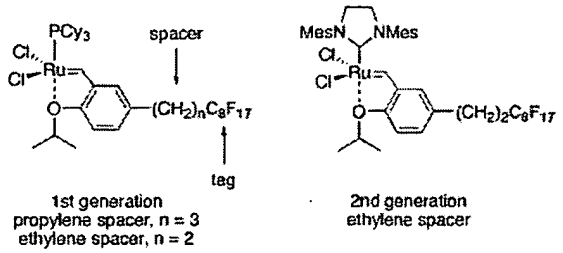

Light fluorous versions of first- and second-generation Grubbs–Hoveyda metathesis catalysts are introduced. These exhibit the expected reactivity profile, are readily recovered from reaction mixtures by fluorous solid-phase extraction, and can be routinely reused five or more times. The catalysts can be used in a stand alone fashion, or supported on fluorous silica gel.

Introduction

Organic molecules bearing small fluorous tags (C_6F_{13}, C_8F_{17}) are called light fluorous molecules.[1] Light fluorous reagents,[2] scavengers, and catalysts are especially convenient since they typically induce reactions of organic substrates under the same conditions as their nonfluorous relatives, but are reliably removed from crude reaction products by fluorous solid-phase extraction (fspe).[3] Only a handful of light fluorous catalysts, including palladium,[4a,b] platinum,[4c] and nickel[4d] complexes, have been described to date.

Alkene metathesis is among the most powerful and popular methods for carbon–carbon bond formation today, and an assortment of metathesis catalysts are now available (Figure 1).[5] Among these, first and second generation Grubbs–Hoveyda catalysts **1**[6] and **2**[7] and related molecules[8] are especially useful because of their scope and stability.[9] The high cost of these catalysts encourages recovery and reuse, even on a small scale.

An assortment of polymer- and ionic liquid-supported metathesis catalysts have been introduced to facilitate separation in metathesis reactions.[10] Recently, Yao has

† Dedicated to Dr. Alfred Bader in celebration of his 80th birthday.

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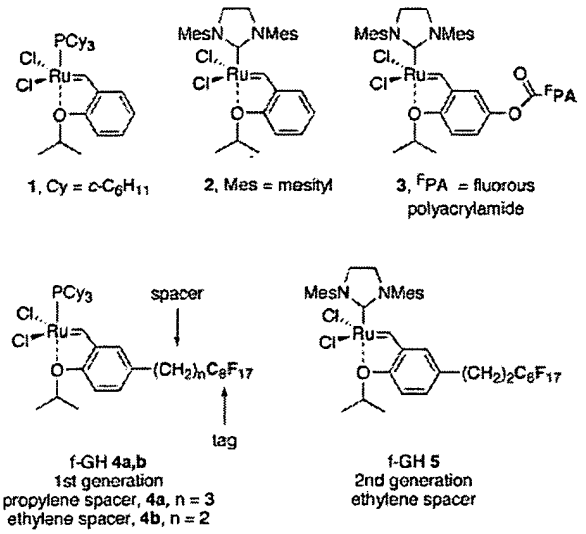


FIGURE 1. Grubbs–Hoveyda (GH) metathesis catalysts.

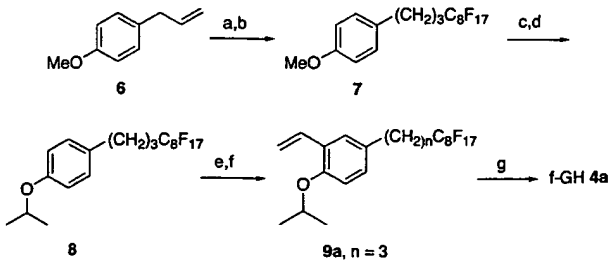
reported a heavy fluorous Grubbs–Hoveyda catalyst **3**.[11] The catalyst is linked to a fluorous polyacrylate and can be used in conjunction with a fluorous solvent for fluorous biphasic catalysis. We report herein complementary light fluorous Grubbs–Hoveyda (f-GH) catalysts **4a,b** and **5**. These induce alkene metathesis reactions under the same conditions as their nonfluorous parents but can be readily separated from crude reaction products by fluorous solid-phase extraction (fspe) when added to reaction mixtures in pure form or by filtration when added in supported form on fluorous silica gel. The catalysts are reasonably stable to both the reaction and separation conditions, and can be recovered and reused repeatedly.

Results and Discussion

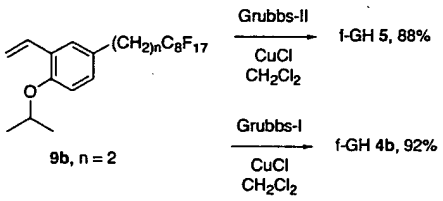
Syntheses of the first- and second-generation f-GH catalysts are summarized in Scheme 1. For first-generation catalyst **4a**, addition of the fluorous tag to 1-allyl-4-methoxybenzene **6** was accomplished by standard atom transfer addition[12] and reduction[13] reactions to provide **7**. Demethylation[14] and isoproylation provided **8**. This was brominated[15] and the bromide was coupled with vinyl tributyltin[16] to provide ligand precursor **9a**. Trans-metathesis[7] with the standard first-generation Grubbs catalyst (Grubbs-I) provided the f-GH catalyst **4a** as brown crystals (mp 159.0–160.0 °C) after recrystallization from CH_2Cl_2/pentane. The crystal structure of this complex was solved, and ORTEP diagrams and full data are provided in the Supporting Information.

SCHEME 1[a]

first generation f-GH catalyst 4a



second generation f-GH catalyst 5 and first generation catayst 4b



[a] Reagents and conditions: (a) 2.2 equiv of $C_8F_{17}I$, 1 equiv of Me_3Al, 5 mol % of $Pd(PPh_3)_4$, CH_2Cl_2, rt, 64% (recrys.); (b) 1.5 equiv of Bu_3SnH, 0.2 equiv of AIBN, benzene, reflux, 81%; (c) 4 equiv of $BBr_3S(CH_3)_2$, dichloroethane, reflux, 88%; (d) 1.5 equiv of NaH, 2 equiv of ^iPrI, THF/DMF, rt, 94%; (e) 1.1 equiv of Br_2, 0.04 equiv of AcOH, CH_2Cl_2, rt, 94%; (f) 50 mol % of $Pd(PPh_3)_4$, 3 equiv of tributylvinylstannane, toulene, reflux, 64%; (g) 1.1 equiv of Grubbs-I, 1.25 equiv of CuCl, CH_2Cl_2, rt, 71%.

Second-generation f-GH catalyst **5** differs from **4a** by having the *N*-heterocyclic carbene (NHC) ligand[17] in place of the phosphine, and it has an ethylene spacer rather than a propylene spacer. The ethylene spacer was used because ligand precursor **9b** became commercially available during the course of this work.[18] Trans-metathesis of **9b** with standard second-generation Grubbs catalyst (Grubbs-II) gave f-GH catalyst **5** as green crystals, mp 136.5–137.5 °C, after column chromatography and recrystallization from CH_2Cl_2/pentane.

Most of the experiments with first generation f-GH catalyst **4a** were complete when styrene **9b** became available to us. However, to show that propylene- and ethylene-spacer catalysts were analogous, we also synthesized **4b** by cross metathesis from **9b** and Grubbs-I catalyst as above. Complex **4b** was isolated in 92% yield as a brown solid, mp 154.5–155.5 °C.

Complexes **4a,b** and **5** were air stable over several days either as solids or dissolved in solvent in an NMR tube, so no special handling or storage precautions were taken. However, **4a** and **5** slowly decomposed over several days when heated in $CDCl_3$ at 80 °C (estimated half-lives: **4a**, ~20 h; **5**, ~8 days). The better thermal stability of **5** is consistent with its better recovery in the reuse experiments described below. The catalysts were not significantly soluble in fluorous solvents such as FC-72 (per-

(10) (a) Nguyen, S. T.; Trnka, T. M. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Vol. 1, pp 61–94. (b) Harned, A. M.; Probst, D. A.; Hanson, P. R. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Vol. 2, pp 361–402.

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(14) Williard, P. G.; Fryhle, C. B. *Tetrahedron Lett.* **1980**, *21*, 3731–3734.

(15) Audic, N.; Clavier, H.; Mauduit, M.; Guillemin, J.-C. *J. Am. Chem. Soc.* **2003**, *125*, 9248–9249.

(16) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508–524.

(17) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900–1923.

(18) (a) Ligand **9b** and FluoroFlash silica gel and TLC plates were purchased from Fluorous Technologies, Inc., www.fluorous.com. FluoroFlash silica gel has a perflouorooctylethyl silyl ($C_8F_{17}CH_2CH_2Si$) bonded phase. (b) DPC holds an equity interest in this company.

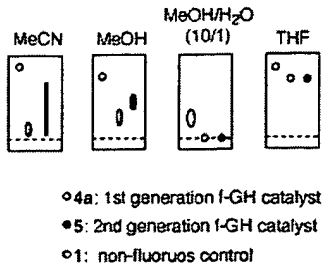


FIGURE 2. TLC behavior of **1**, **4a**, and **5** on FluoroFlash silica.

fluorohexanes), but instead dissolved in common organic solvents including diethyl ether, THF, CH_2Cl_2, and CH_3CN.

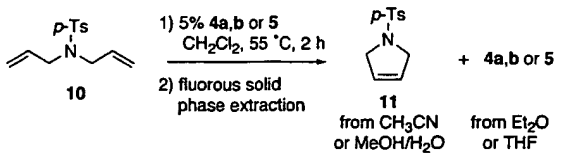
To evaluate prospects for fspe separation, we analyzed the TLC behavior of the standard and fluorous GH catalysts under typical "fluorophobic" conditions (to model the first stage of a fluorous spe) and "fluorophilic" conditions (to model the second stage) on commercial FluoroFlash fluorous silica gel.[18] The results of these informative experiments are summarized pictorially in Figure 2.

When the FluoroFlash TLC plate was eluted with 100% acetonitrile, nonfluorous catalyst **1** moved with the solvent front, as expected, while f-GH catalyst **4a** was well retained. In contrast, f-GH catalyst **5** exhibited a long streak, suggesting decomposition. In 100% methanol, both f-GH catalysts **4a** and **5** provided well-resolved spots, but the retention factors (R_f) were too high for filtration-based separation. In 10/1 MeOH/H_2O, the R_f factors of both complexes decreased significantly and they only barely moved from the baseline. In the fluorophilic solvent THF, both complexes exhibited clean spots near the solvent front. A similar behavior was observed in ether (not shown).

These results suggest that complex **4a** can be retained in a fluorophobic pass with water-free acetonitrile while aqueous methanol is preferred for **5**. Both complexes should be eluted in a fluorophilic pass with ether or THF. These experiments show how simple fluorous TLC experiments can be used to quickly identify suitable conditions for solid-phase extractions.

The reaction, separation, and reuse features of f-GH catalysts **4a** and **5** were studied in detail in the conversions of *N*,*N*-diallyl-*p*-toluenesulfonamide **10** to *N*-*p*-tosyl-2,5-dihydro-1*H*-pyrrole **11**, and the results of this series of experiments are summarized in Table 1. In a typical experiment with the first-generation catalyst **4a**, 196 mg (0.8 mmol) of **10** was heated with 41 mg (5 mol %) of **4a** in dichloromethane at reflux for 2 h.[19] The cooled mixture was loaded to 1.2 g of fluorous silica gel (30× weight of the catalyst), which was eluted with 6 mL of acetonitrile to provide an organic fraction containing product **11** (180 mg, >99%) followed by 18 mL of ether to provide a fluorous fraction containing recovered catalyst **4** (36 mg, 88%).

TABLE 1. Reuse of f-GH Catalysts 4a,b and 5 in the Metathesis of 10 to 11



entry	cat.	cyc	10 mg	cat mg	**11**,% (mg)	cat., % (mg)
1	**4a**	1	196	41	99 (180)	88 (36)
2	**4a**	2	170	36	99 (155)	72 (26)
3	**4a**	3	90	19	98 (78)	84 (16)
4	**4a**	4	76	16	99 (67)	69 (11)
5	**4a**	5	52	11	99 (46)	73 (8.0)
6	**4a**	6	28	6	99 (25)	73 (4.4)
7	**4a**	7	21	4	98 (18)	80 (3.2)
8	**4b**	1	121	25	99 (107)	84 (21)
9	**5**	1	300	64	96 (256)	91 (58)
10	**5**	2	249	53	98 (217)	91 (48)
11	**5**	3	215	46	98 (187)	85 (39)
12	**5**	4	161	35	94 (134)	89 (31)
13	**5**	5	140	30	97 (121)	90 (27)

The recovered catalyst exhibited a ^1H NMR spectrum similar to the starting catalyst, and it was used directly in the second cycle with appropriate adjustment of all other components to maintain the same ratio (5 mol % of catalyst). This process was continued through seven cycles with the weights and yields of product and catalyst shown in Table 1, entries 1−7. The yield of the product was uniformly high, while the yield of recovered catalyst ranged from 69% to 88%. At the end of the seventh cycle, about 10% of the original catalyst was recovered. While the recovered complex is no longer pristine (see the Supporting Information for the ^1H NMR spectrum), we believe that it is still active. Overall, the initial 41 mg of catalyst (0.04 mmol) was used to metathesize 633 mg (about 2.5 mmol) of **10**. No effort for further optimization of the loading or recovery was attempted.

The first-generation catalyst with the ethylene spacer **4b** was tested in a single experiment (entry 8) and gave results very comparable to those of **4a**. Based on this and the structural similarity, we suggest that **4a** and **4b** can be used interchangeably.

The second-generation catalyst **5** behaved similarly, and a series of five metathesis cycles with this catalyst are summarized in Table 1, entries 9−13.[20] Optimized fspe conditions required somewhat more fluorous silica gel (50× weight of the catalyst) compared to **4a**. The fluorophobic elution was conducted with 80% MeOH/H_2O and THF was used for the fluorophilic elution. Yields of product **11** were again high (94−98%) in each cycle, while

(19) Tosyl amide **10** (1.00 g, 3.98 mmol) and **4a** (211 mg, 0.199 mmol, 0.050 equiv) and dichloromethane (79.6 mL, 0.05 M) were placed in a flask under an argon atmosphere and the mixture was refluxed for 2 h at 55 °C. After removal of the volatile components by evaporation, the brownish mixture was submitted to separation by fspe. A short column was packed with fluorous silica gel (6.3 g) using acetonitrile as the solvent. The crude reaction mixture was then loaded onto this column and eluted with 31.5 mL of acetonitrile to give RCM product **11** in 98% yield (865 mg). The next elution of diethyl ether (94.5 mL) afforded the catalyst **4a** in 87% yield (184 mg).

(20) Tosyl amide **10** (300 mg, 1.20 mmol) and **5** (64.2 mg, 0.060 mmol, 0.050 equiv) and dichloromethane (24 mL, 0.05 M) were placed in a flask under an argon atmosphere and the mixture was refluxed for 2 h at 55 °C. After removal of the volatile components by evaporation, the brownish mixture was submitted to separation by fspe. A short column was packed with fluorous silica gel (3.2 g) using aq 80% MeOH as the solvent. The crude reaction mixture was then loaded onto this column and eluted with 16.1 mL of aq 80% MeOH and successively 9.7 mL of THF. The evaporation of the 80% MeOH fraction and the THF fraction by vacuum centrifuge gave RCM product **11** in 96% yield (256 mg) and catalyst **5** in 91% yield (58.3 mg), respectively.

the recovery of catalyst **5** was better, ranging from 85% to 91%. At the end of five cycles, 915 mg (4.1 mmol) of product **11** was produced starting from 64 mg (0.06 mmol) of **5**, and 42% of the original catalyst mass was recovered. The catalyst recovered after cycle five is not as pure as the starting complex (see ^{1}H NMR spectra in the Supporting Information), but we expect that it is still active. And if desired, it could be repurified by chromatography or crystallization prior to reuse.

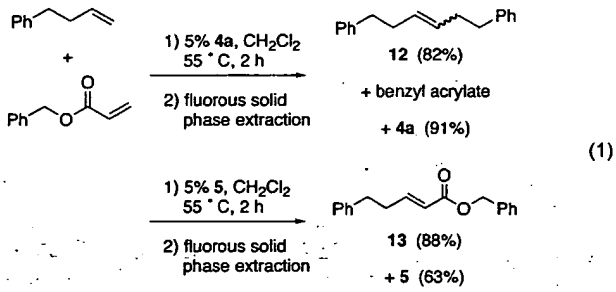
The ^{1}H NMR spectra of the products of Table 1 are clean and ligand resonances cannot be detected in either these or the ^{19}F NMR spectra (see the Supporting Information). However, the crude products are typically light tan. This, coupled with the observation that the recovered yield of the catalyst is never quantitative, suggests that the product may still contain small amounts of ruthenium. To obtain more information on residual ruthenium, we metathesized 1 g of substrate **10** with 211 mg (5 mol %) of f-GH catalyst **4a** under the standard conditions. After fspe, we recovered 965 mg (98%) of **11** along with 184 mg (87%) of the catalyst **4a**.

Crude product **11** was light tan in color, though no resonances for the ligand could be detected in either its ^{1}H or ^{19}F NMR spectrum. Spiking the product with 0.3 mol % of benzotrifluoride (an amount equivalent to 6% of the original amount of catalyst) showed that the CF_3 group of the spike was readily detected, so the fluorine content of the sample must be well below this. Elemental analysis of the crude product showed that it contained 0.15% ruthenium, which corresponds to about 6% of the original ruthenium added.[21] Because the corresponding 6% of the ligand is absent, we presume that most of this is ruthenium that has been released from the fluorous component of the ligand and is therefore not retained on the spe. Portions of the crude product were further purified by recrystallization (to give a very faint tan solid) and flash chromatography (to give a white solid). These products exhibited <0.05% ruthenium (the limit of delectability) in elemental analysis. These levels were deemed satisfactory and further trace analysis was not conducted. A similar preparative experiment with **5** gave qualitatively similar results.[22]

The scope of the new catalysts was briefly probed by conducting ring closing metathesis with five substrates under the standard conditions, and the results of these experiments are summarized in Table 2. All five substrates cyclized smoothly and in good yield with f-GH catalyst **4a**, though the cyclization of acrylate in entry 3 required 3 days. Yields of products were uniformly good (84–99%), and the catalyst was recovered in 76–92% yields. Metathesis of substrate in entry 5 was described with an ionic liquid-supported first-generation GH catalyst, but deactivation of the catalyst was observed in the third cycle.[14] We conducted three cycles of metathesis of this substrate without problem, and recovered 70% of the original catalyst mass.

Catalyst **5** was more reactive as expected, and all substrates were consumed in 2 h. However, only the products in entries 1–3 were reasonably pure as assayed by ^{1}H NMR spectroscopy. The target products from entries 4 and 5 were indeed the major components, but these samples also had significant impurities that may result from ring opening metathesis or polymerization. These products were not further purified. Recovery of the catalyst **5** was satisfactory in entries 1–4 (76–89%), but lower (62%) in entry 5.

Next, we tested the reactivity of **4a** and **5** in a representative cross-metathesis reaction between 4-phenyl-1-butene and benzyl acrylate under the standard conditions with the usual fspe separation (eq 1). First-



(1)

generation catalyst **4a** provided the homodimer **12** in 82% yield alongside recovered benzyl acrylate (100%) and catalyst **4a** (91%). Second-generation catalyst **5** provided cross-coupled product **13** in 88% yield and homodimer **12** was not detected by ^{1}H NMR spectroscopy. Catalyst **5** was recovered in 63% yield. These results are in line with expectations from the nonfluorous catalysts[6,7,23] and provide additional evidence that the fluorous catalysts will exhibit reactivity profiles that can be readily anticipated from results in the standard series.

Finally, we conducted a series of experiments with a silica-supported catalyst to show that f-GH catalysts are compatible with this mode of delivery and removal. Recently, Gladysz, Bannwarth, and others have developed procedures to isolate supported fluorous compounds from reactions,[24] and Teflon and fluorous silica have been used as supports to date. In some procedures, the supported catalyst or reactant is added directly to the reaction mixture, while in others a soluble catalyst or reactant is used and the support is added after the reaction. This later approach is one of the standard ones for spe loading.[25]

(21) A control experiment with standard catalyst **1** (14 mg) and **10** (119 mg) provided 109 mg of crude product **11** (>100%). This was a dark brown solid and was contaminated with 0.56% ruthenium, corresponding to 25% of the original amount of ruthenium added. Surprisingly, 10 mg (71%) of the original catalyst was recovered from the fluorous spe. The TLC results (Figure 2) suggest that the catalyst should not be retained, so this may be due to precipitation during spe loading or elution.

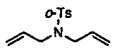
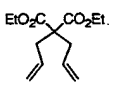
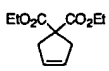
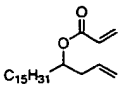
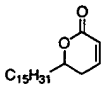
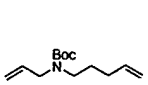
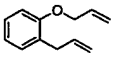
(22) The crude product **11** was light tan and contained 0.46% Ru by elemental analysis (19% of original catalyst charge; however, there may be an error in this analysis since 91% of the original catalyst mass was recovered). The chromatographed product was a white powder containing <0.09% Ru while the crystallized product was a very pale tan powder containing <0.05% Ru.

(23) (a) Chaterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11, 360–11, 370. (b) Fürstner, A.; Ackermann L.; Gabor, B.; Goddard, R.; Lehmann, C. W.; Mynott, R.; Stelzer, F.; Thiel, O. R. *Chem. Eur. J.* **2001**, *7*, 3236–3253.

(24) (a) Schwinn, D.; Glatz, H.; Bannwarth, W. *Helv. Chim. Acta* **2003**, *86*, 188–195. (b) Tzschucke, C. C.; Markert, C.; Glatz, H.; Bannwarth, W. *Angew. Chem., Int. Ed.* **2002**, *41*, 4500–4503. (c) Wende, M.; Meier, R.; Gladysz, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 11490–11491. (d) Wende, M.; Gladysz, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 5861–5872. (e) Jenkins, P. M.; Steele, A. M.; Tsang, S. C. *Catal. Commun.* **2003**, *4*, 45–50.

(25) See Fluoruos Technolgies, Inc. Product Application Note "Fluorous Solid-Phase Extraction": http://fluorous.com/download.html.

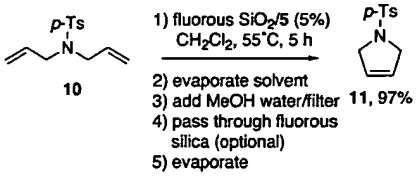
TABLE 2. Examples of RCM with f-GH Catalysts 4a and 5

Entry	Substrate	Product	cat	time (h)	%yld prod	%yld cat
1			**4a**	2	98	92
			5	2	92	76
2			**4a**	2	99	88
			5	2	95	80
3			**4a**	72	90	76
			5	2	82	83
4			**4a**	4	87[a] (67[c])	83
			5	2	92[a]	89
5			**4a**[b]	2	84	89
			4a[b]	2	89	83
			4a[b]	2	82	95
			5	2	51[a]	62

[a] Contains impurities. [b] Three cycles with the same original catalyst charge. [c] After flash chromatographic purification.

We initially dissolved f-GH complex **5** in CH_2Cl_2, added 30× weight of fluorous silica gel, and then evaporated to dryness. The resulting green, free-flowing supported complex was then suspended in 80% MeOH/water. The powder remained green while the solution stayed clear; little or no reaction occurred when substrates were added followed by heating. As expected, the complex prefers the fluorous silica to the polar, hydrophilic solvent. However, the complex is readily extracted back from the fluorous silica by washing with the standard reaction solvent dichloromethane. Thus, simply by switching solvents, the complex can be driven onto or extracted off of the fluorous silica gel.

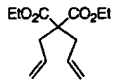
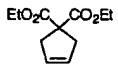
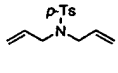
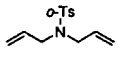
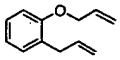
Equation 2 summarizes a very simple procedure that we developed to capitalize on this two-state, solvent-dependent behavior. Silica-supported **5** (180 mg of silica



(2)

containing 6 mg of **5**, 5 mol %) was added to **10** (28 mg) in CH_2Cl_2 (2.2 mL). The resulting slurry was refluxed for 5 h, then the mixture was cooled and the solvent was evaporated to yield a dry green powder. Methanol/water (80%, 3 mL) was added and the slurry was filtered with a standard suction filter. The liquid phase containing the product was clear to the naked eye, yet it still contains a trace (<1%, see below) of the originally added catalyst.

TABLE 3. Examples of RCM with Silica-Supported f-GH Catalyst 5

Entry	Substrate	Product	time (h)	%yld prod	^{19}F NMR res?[a]
					
1			1	97	Yes
2			1	98	Yes
3			1	98[b]	Yes
4			3	94	Yes[c]
5			5	97	Yes
6			6	96	No
7			2	67	Yes

[a] Yes: trace signals detected in the ^{19}F NMR, estimated less than 0.4% compared to the product. No: no clear signals in the ^{19}F NMR spectrum. [b] At 85% conversion of **10**. [c] Contains 0.4% signal relative to the product

This material may be of sufficient purity for many uses; however, to upgrade it even further, we poured the MeOH/water solution through a small pad (60 mg) of additional fluorous silica gel. Although the solution appeared clear, a faint green line was visible at the top of the silica pad after filtration. Product **11** (24 mg, 97%) was obtained after evaporation of the solvent, and it was fluorine free according to the standard ^{19}F NMR analysis. The green silica gel from the initial filtration was washed with THF to provide the recovered catalyst **5** in 83% yield after evaporation.

Table 3 summarizes the results of several experiments conducted to probe the features of supported catalyst **5**. In these experiments, the slurry resulting from addition of MeOH/water was simply filtered and evaporated; it was not passed through an additional pad of fluorous silica. Diethyl diallyl malonate was subjected to three cycles of metathesis using the same supported catalyst charge (entries 1–3). Unlike the experiments in Table 2, we did not adjust the amount of precursor to compensate for lost catalyst (because the supported catalyst is a material and we do not know how much catalyst was lost); we simply used the same amount of precursor in each of the three cycles. Cycles 1 and 2 proceeded smoothly in the allotted time (1 h), while only 85% conversion was observed in cycle 3. Presumably this is a result of the gradual erosion of the catalyst, as in Table 2. A fourth cycle (entry 4) was conducted for 3 h, and this gave complete conversion to **11**, which was isolated in 94% yield.

All of the crude products contained tiny, but clearly visible resonances in the ^{19}F NMR spectra, which we estimate to account for less than 8% of the original amount of catalyst **5** that was added (in other words, less than 0.4 mol % compared to the product). This estimate is based on an accurate quantitation of the product of entry 4 by adding a BTF standard; this contained 0.4% of the original product. While the ^{19}F NMR assay quantities total fluorine content and does not provide structural information, we speculate that most of the trace fluorine-containing material is the catalyst because of the green band observed in filtration (see above).

Fresh fluorous silica-supported catalyst charges were used to metathesize the substrates in entries 5–7, and yields were uniformly excellent. Purities were also satisfactory, with very small ligand peaks (again possibly from the catalyst) being detected in the products from entries 5 and 7. The ^{19}F NMR from entry 6 was free from resonances. The colors of all the products were very pale tan and we judged these products to be more faintly colored than typical products from crude fspes (Table 2). The very small amounts of fluorine-containing residues in these samples are acceptable for many applications; indeed, it is only the high sensitivity of the assay that allows us to detect these otherwise spectroscopically silent contaminants. If better quality product is needed, it can be filtered through a small pad of fluorous silica gel to remove the last traces of fluorous residues.

We conducted a series of control experiments with diallyl malonate to better understand the supported procedure, and the results of these experiments are summarized in the Supporting Information. Briefly, attempts to use the standard Grubbs–Hoveyda catalyst **2** under the procedure outlined above with fluorous silica gel, reverse phase silica gel, or no silica gel at all were uniformly unsuccessful. The standard catalyst **2** simply dissolved when the 80/20 MeOH/water was added, and it ended up contaminating the product. Little or no catalyst was retained on the support or left in the flask (when support was absent).

In contrast, while the use of f-GH catalyst **5** supported on standard silica gel gave inferior results, its use supported on reverse phase silica gel or unsupported gave comparable results to the use of fluorous-supported catalyst. In the unsupported procedure, the catalyst was simply precipitated by addition of 80/20 MeOH/water, but its recovery was difficult since it clung to the flask and the stir bar. These results suggest that the prime factor behind the success of the separation in the solvent-switch procedure is the insolubility of **5** in 80/20 MeOH/water. This is not surprising, since the same insolubility drives the related fspe. Because of the mutually selective nature of fluorous interactions, we recommend fluorous silica gel as the material of first choice for this procedure, though other materials or even no material at all can potentially be used.

Conclusions

New fluorous Grubbs–Hoveyda catalysts **4a,b** and **5** show typical features of light fluorous catalysts; they react under similar conditions and show similar reactivity profiles to the nonfluorous analogues, but they are readily separated and recovered either by filtration (when added initially on fluorous silica gel) or by fluorous solid-phase extraction (when used in a standard solution-phase reaction). Only a small amount of fluorous silica gel is needed (30–50× weight of the catalyst), and catalysts **4a,b** are especially convenient because they can be retained under water-free conditions with acetonitrile. While most of the work on first-generation catalysts has been conducted with propylene-spaced complex **4a**, the commercial availability of the styrene precursor **9b** of ethylene-spaced complex **4b** and the similarities between **4a** and **4b** suggest that **4b** is presently the catalyst of choice in this series.

Standard Grubbs–Hoveyda catalysts can often be removed from crude reaction products by regular silica gel chromatography,[6,7] but this method is probably not as reliable or general as the fluorous spe; some organic molecules will have similar R_f values to standard catalysts on regular silica gel while essentially no organic molecules will be retained on fluorous spe. Furthermore, we find that both fluorous and nonfluorous Grubbs–Hoveyda catalysts tend to streak to some extent on standard silica gel. This suggests that purification of products that elute after the complexes can be a problem in standard silica gel chromatography. In contrast, on fluorous silica gel, no product ever elutes after the complex. This "one size fits all" aspect of the fluorous spe is attractive.

The recoveries of the catalyst are good (typically 75–95%) but not quantitative, at least in part because the catalysts are not fully stable to the reaction conditions. Small amounts of ruthenium are divorced from the fluorous carbene ligand during the reaction and leach into the product. The levels of contamination are tolerable for many types of multistep syntheses and can be reduced by chromatography, crystallization, or other means. On the positive side, because the fluorous spe targets a ligand and not the metal, the material recovered from the spe is largely active catalyst. In addition to reusing the catalyst, we routinely reused the fluorous silica gel after washing with THF and reconditioning with the fluorophobic solvent.

Assorted resin-bound,[9] heavy fluorous[10] and ionic liquid-supported[14] Grubbs catalysts have been reported, and these catalysts are effectively materials. Analyses of these materials are typically based on performance. This is convenient when the material is reused to repeatedly conduct the same reaction, but has detractions when the material is used to conduct different reactions. For example, degraded catalyst products or left over products or reactants from a prior reaction may remain in the active catalyst material and contaminate subsequent reactions. In contrast, the light fluorous catalysts are molecules, and can be analyzed and characterized as such. The purity of the recovered catalyst is readily assessed by NMR spectroscopy, melting point, and other means. If this is deemed unacceptable, then the catalyst can be recrystallized or otherwise purified. Standard Grubbs–Hoveyda catalysts are expensive even in small quantities, so the ability to recover and reuse the catalyst can result in significant cost savings.

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Supporting Information Available: Procedures for reactions and spe purifications, spectroscopic data for products, data for the crystal structure of **4a**, and copies of NMR spectra of typical products after spe. This material is available free of charge via the Internet at http://pubs.acs.org.

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